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(54) Title: 1-HETEROCYCLE SUBSTITUTED DIARYLAMINES

(57) Abstract

1-Heterocycle substituted diarylamines, methods of making and using them, and compositions containing them.

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1-HETEROCYCLE SUBSTITUTED DIARYLAMINES

This invention relates to diaryl amines such as 1-heterocycle substituted diarylamines.

BACKGROUND

MEK enzymes are dual specificity kinases involved in, for example, immunomodulation, inflammation, and proliferative diseases such as cancer and restenosis.

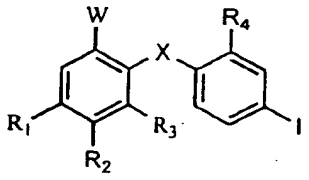
Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Defects include a change either in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade . The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, a G-protein that is activated when bound to GTP, and inactivated when bound to GDP. The above-mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras-GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras-GTP for its own activation is the Raf family. These in turn activate MEK (e.g., MEK_1 and MEK_2) which then activates MAP kinase, ERK (ERK_1 and ERK_2). Activation of MAP kinase by mitogens appears to be essential for proliferation; constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, for example by use of a

dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S^{218} and S^{222} in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y^{185}, and a threonine residue, T^{183}, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold. Activated MAP kinase can then catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, such as a kinase, a transcription factor, or another cellular protein. In addition to Raf-1 and MEKK, other kinases activate MEK, and MEK itself appears to be a signal integrating kinase. Current understanding is that MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than the MAP kinase , ERK, has been demonstrated to date and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

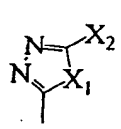
SUMMARY

The invention features a compound having the formula (I) below:

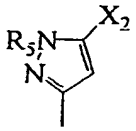


I

W is one of the following formulae (i) – (xiii):



(i)



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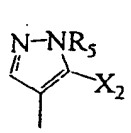

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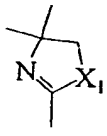

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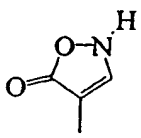

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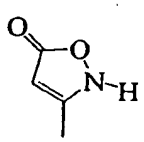

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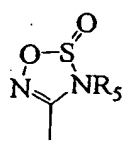

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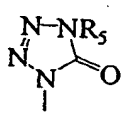

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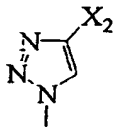

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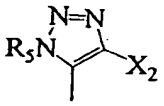

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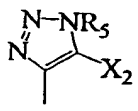

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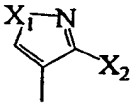

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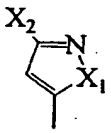

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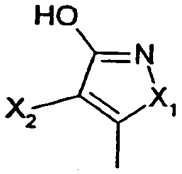

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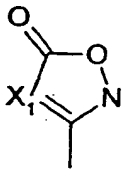
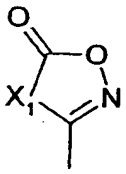


(xv)



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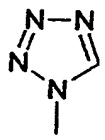

(xvii)

X_1 is O, S, or NR_F. X_2 is OH, SH, or NHR_E. Each of R_E and R_F is H or C_{1-4} alkyl; each of R_1 and R_2 is independently selected from H, F, NO_2, Br and Cl; R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole. R_3 is selected from H and F; each of R_G, R_H, and R_4 is independently selected from H, Cl and CH_3. R_5 is H or C_{1-4} alkyl. Each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO_2. Each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-4} alkenyl, C_{3-4} alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO_2, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C_{1-2} alkyl, hydroxyl, amino, and NO_2. The invention also features a pharmaceutically acceptable salt or C_{1-8} ester of a disclosed compound. For example, the disclosed alcohol compounds may form esters having the structure obtained by replacing the H of a hydroxyl group with a $-C(=O)C_{1-7}$ acyl group.

The invention also relates to a pharmaceutical composition including (a) a compound of formula (I) and (b) a pharmaceutically-acceptable carrier.

The invention further relates to a method for treating proliferative diseases, such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis. Other aspects of the invention include methods for treating MEK-related (including ras-related) cancers, whether solid or hematopoietic. Examples of cancers include colorectal, cervical, breast, ovarian, brain, acute leukemia, gastric, non-small cell lung, pancreatic, and renal cancer. Further aspects of the invention include methods for treating or reducing the symptoms of xenograft (cell(s), skin, limb, organ or bone marrow transplant) rejection, osteoarthritis, rheumatoid arthritis, cystic fibrosis, complications of diabetes (including diabetic retinopathy and diabetic nephropathy), hepatomegaly, cardiomegaly, stroke (such as acute focal ischemic stroke and global cerebral ischemia), heart failure, septic

shock, asthma, and Alzheimer's disease. Compounds of the invention are also useful as antiviral agents for treating viral infections such as HIV, hepatitis (B) virus (HBV), human papilloma virus (HPV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). These methods include the step of administering to a patient in need of such treatment, or suffering from such a disease or condition, a pharmaceutically-effective amount of a disclosed compound or pharmaceutical composition thereof.

The invention also features methods of combination therapy, such as a method for treating cancer, wherein the method further includes providing radiation therapy or chemotherapy, for example, with mitotic inhibitors such as a taxane or a vinca alkaloid. Examples of mitotic inhibitors include paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine. Other therapeutic combinations include a MEK inhibitor of the invention and an anticancer agent such as cisplatin, 5-fluorouracil or 5-fluoro-2-4(1H,3H)-pyrimidinedione (5FU), flutamide, and gemcitabine.

The chemotherapy or radiation therapy may be administered before, concurrently, or after the administration of a disclosed compound according to the needs of the patient.

The invention also features synthetic intermediates and methods disclosed herein.

Other aspects of the invention are provided in the description, examples, and claims below.

DETAILED DESCRIPTION

The invention features diaryl amine compounds, pharmaceutical compositions thereof, and methods of using such compounds and compositions.

According to one aspect of the invention, the compounds are MEK inhibitors. MEK inhibition assays include the *in vitro* cascade assay for inhibitors of MAP kinase pathway described at column 6, line 36 to column 7, line 4 of U.S. Patent Number 5,525,625 and the in vitro MEK assay at column 7, lines 4-27 of the same patent, the entire disclosure of which is incorporated by reference (see also Examples 9-12 below).

A. Terms

Certain terms are defined below and by their usage throughout this disclosure.

Alkyl groups include aliphatic (i.e., hydrocarbyl or hydrocarbon radical structures containing hydrogen and carbon atoms) with a free valence. Alkyl groups are understood to include straight chain and branched structures. Examples include methyl, ethyl, propyl, isopropyl, butyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, 2,3-dimethylpropyl, hexyl, 2,3-dimethylhexyl, 1,1-dimethylpentyl, heptyl, and octyl. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

Alkyl groups can be substituted with 1, 2, 3 or more substituents which are independently selected from halo (fluoro, chloro, bromo, or iodo), hydroxy, amino, alkoxy, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, arylalkyloxy, heterocyclic radical, and (heterocyclic radical)oxy. Specific examples include fluoromethyl, hydroxyethyl, 2,3-dihydroxyethyl, (2- or 3-furanyl)methyl, cyclopropylmethyl, benzyloxyethyl, (3-pyridinyl)methyl, (2- or 3-furanyl)methyl, (2-thienyl)ethyl, hydroxypropyl, aminocyclohexyl, 2-dimethylaminobutyl, methoxymethyl, *N*-pyridinylethyl, diethylaminoethyl, and cyclobutylmethyl.

Alkenyl groups are analogous to alkyl groups, but have at least one double bond (two adjacent sp^2 carbon atoms). Depending on the placement of a double bond and substituents, if any, the geometry of the double bond may be *entgegen* (E), or *zusammen* (Z), *cis*, or *trans*. Similarly, alkynyl groups have at least one triple bond (two adjacent sp carbon atoms). Unsaturated alkenyl or alkynyl groups may have one or more double or triple bonds, respectively, or a mixture thereof; like alkyl groups, unsaturated groups may be straight chain or branched, and they may be substituted as described both above for alkyl groups and throughout the disclosure by example. Examples of alkenyls, alkynyls, and substituted forms include cis-2-butenyl, trans-2-butenyl, 3-butynyl, 3-phenyl-2-propynyl, 3-(2'-fluorophenyl)-2-propynyl, 3-methyl(5-phenyl)-4-pentynyl, 2-hydroxy-2-propynyl, 2-methyl-2-propynyl, 2-propenyl, 4-hydroxy-3-butynyl, 3-(3-

fluorophenyl)-2-propynyl, and 2-methyl-2-propenyl. In formula (I), alkenyls and alkynyls can be C_{2-4} or C_{2-8}, for example, and are preferably C_{3-4} or C_{3-8}.

More general forms of substituted hydrocarbon radicals include hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, and corresponding forms for the prefixes amino-, halo- (e.g., fluoro-, chloro-, or bromo-), nitro-, alkyl-, phenyl-, cycloalkyl- and so on, or combinations of substituents. According to formula (I), therefore, substituted alkyls include hydroxyalkyl, aminoalkyl, nitroalkyl, haloalkyl, alkylalkyl (branched alkyls, such as methylpentyl), (cycloalkyl)alkyl, phenylalkyl, alkoxy, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, aryloxyalkyl, arylalkyloxyalkyl, (heterocyclic radical)alkyl, and (heterocyclic radical)oxyalkyl. R_1 thus includes hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, hydroxycycloalkyl, hydroxyaryl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminocycloalkyl, aminoaryl, alkylalkenyl, (alkylaryl)alkyl, (haloaryl)alkyl, (hydroxyaryl)alkynyl, and so forth. Similarly, R_A includes hydroxyalkyl and aminoaryl, and R_B includes hydroxyalkyl, aminoalkyl, and hydroxyalkyl(heterocyclic radical)alkyl.

Heterocyclic radicals, which include but are not limited to heteroaryls, include: furyl, oxazolyl, isoxazolyl, thiophenyl, thiazolyl, pyrrolyl, imidazolyl, 1,3,4-triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, indolyl, and their nonaromatic counterparts. Further examples of heterocyclic radicals include piperidyl, quinolyl, isothiazolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyrrolyl, pyrrolidinyl, octahydroindolyl, octahydrobenzothiofuranyl, and octahydrobenzofuranyl.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000 or less than that of its IC_{50} or one or more of the above-named enzymes.

B. Compounds

One aspect of the invention features the disclosed compounds shown in formula (I) in the Summary section.

Embodiments of the invention include compounds wherein: (a) R_1 is bromo or chloro; (b) R_2 is fluoro; (c) R_3 is H; (d) each of R_2 and R_3 is H; (e) each of R_2 and R_3 is fluoro; (f) R_1 is bromo; (g) each of R_1, R_2 and R_3 is fluoro; (h) R_2 is nitro; (i) R_3 is H; (j) R_4 is chloro; (k) R_4 is methyl; (l) R_5 is H; (m) R_5 is CH_3; (n) X_1 is O or S; (o) X_1 is NH or NCH_3; (p) X_2 is OH, SH, or NH_2; (q) X_2 is OH; (r) X_2 is NHR_E; (s) R_4 is H; (t) R_4 is chloro or methyl; or combinations thereof.

Preferably, where one of the substituents on a heterocyclic radical is an alkenyl or alkynyl group, the double or triple bond, respectively, is not adjacent the point of attachment when it is a heteroatom. For example, in such a situation, the substituent is preferably prop-2-ynyl, or but-2 or 3-enyl, and less preferably prop-1-ynyl or but-1-enyl.

Examples of compounds include: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)- amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-

phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; and 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

Further examples include: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-

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phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

The invention also features compounds such as: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-

dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; and 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

Further examples of the invention include 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2l>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; and 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

Further compounds, where R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole, include the following groups:

Group 1

(1) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-[2-(2-methoxy-ethoxy)-ethyl]-benzenesulfonamide

(6) N-(2-Dimethylamino-ethyl)-2-fluoro-5-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-iodo-phenylamino)-N-methyl-benzenesulfonamide

Group 2

(1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 2b

(1) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-N-methyl-N-(3-morpholin-4-yl-propyl)-benzenesulfonamide

(3) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-N-[3-(4-methyl-piperazin-1-yl)-propyl]-benzenesulfonamide

(6) 5-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-N-(3-piperidin-1-yl-propyl)-benzenesulfonamide

Group 3

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(2) 2-Fluoro-5-(4-iodo-phenylamino)-4-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-benzenesulfonamide

Group 4

(1) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(5-hydroxy-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 2-Fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1,3,4-thiadiazol-2-yl)-benzenesulfonamide

Group 5

(1) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(5-Amino-1,3,4-thiadiazol-2-yl)-5-(4-iodo-phenylamino)-2-mercapto-benzenesulfonamide

(3) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(5-Amino-1,3,4-thiadiazol-2-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 6

(1) 2-Fluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(5-hydroxy-4H-1,2,4-triazol-3-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[4-(2-Dimethylamino-ethyl)-5-hydroxy-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-4-methyl-4H-1,2,4-triazol-3-yl)-benzenesulfonamide

Group 7

(1) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(5-Amino-4H-1,2,4-triazol-3-yl)-2-fluoro-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-[5-Amino-4-(3-dimethylamino-propyl)-4H-1,2,4-triazol-3-yl]-2-fluoro-4-(4-iodo- phenylamino)-benzenesulfonamide

(5) 5-(5-Amino-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(5-Amino-4-methyl-4H-1,2,4-triazol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 8

(1) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 2-Fluoro-4-(3-hydroxy-isoxazol-5-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 2-Fluoro-5-(3-hydroxy-isoxazol-5-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-5-yl)-benzenesulfonamide

Group 9

(1) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(3-Amino-isoxazol-5-yl)-2-bromo-5-(4-iodo-phenylamino)-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-5-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-5-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(5) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(6) 5-(3-Amino-isoxazol-5-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

Group 10

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

(6) 2-Bromo-5-(4-iodo-phenylamino)-4-(3-mercapto-isoxazol-5-yl)-benzenesulfonamide

Group 11

(1) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-hydroxy-isoxazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(3-hydroxy-isoxazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Bromo-4-(3-hydroxy-isoxazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 12

(1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 13

(1) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(3-Amino-isoxazol-4-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(3-Amino-isoxazol-4-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide"

(5) 5-(3-Amino-isoxazol-4-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(3-Amino-isoxazol-4-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 14

(1) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2-fluoro-benzenesulfonamide

(3) 5-(2-Amino-5H-pyrrol-3-yl)-2,3-difluoro-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 5-(2-Amino-5H-pyrrol-3-yl)-4-(2-chloro-4-iodo-phenylamino)-2,3-difluoro-benzenesulfonamide

(5) 5-(2-Amino-5H-pyrrol-3-yl)-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 4-(2-Amino-5H-pyrrol-3-yl)-2-chloro-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 15

(1) 2-Fluoro-5-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-1H-pyrazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-{5-hydroxy-1-[3-(4-methyl-piperazin-1-yl)-propyl]-1H-pyrazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-4-(5-hydroxy-1H-pyrazol-4-yl)-5-(4-iodo-phenylamino)-benzenesulfonamide

Group 16

(1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

Group 17

(1) 2-Fluoro-5-(5-hydroxy-3-methyl-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-2-methyl-phenylamino)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-5-(5-hydroxy-3H-1,2,3-triazol-4-yl)-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-{5-hydroxy-3-[2-(2-methoxy-ethoxy)-ethyl]-3H-1,2,3-triazol-4-yl}-4-(4-iodo-phenylamino)-benzenesulfonamide

Group 18

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(6) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 19

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)- benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

(5) 5-[4-(2-Dimethylamino-ethyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-2-fluoro-4-(4-iodo-phenylamino)-benzenesulfonamide

(6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(4-methyl-5-oxo-4,5-dihydro-tetrazol-1-yl)-benzenesulfonamide

Group 20

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(4) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 2-Fluoro-4-(4-iodo-phenylamino)-5-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(6) 2-Fluoro-5-(4-iodo-phenylamino)-4-(2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 21

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-N-methyl-5-(3-methyl-2-oxo-2,3-dihydro-1,2,3,5-oxathiadiazol-4-yl)-benzenesulfonamide

Group 22

(1) 2-Fluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(2) 2,6-Difluoro-3-(4-iodo-phenylamino)-4-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(3) 2,3-Difluoro-4-(4-iodo-2-methyl-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(4) 2-Fluoro-4-(4-iodo-phenylamino)-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(5) 4-(2-Chloro-4-iodo-phenylamino)-2,3-difluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

(6) 4-(2-Chloro-4-iodo-phenylamino)-2-fluoro-5-(5-oxo-2,5-dihydro-isoxazol-3-yl)-benzenesulfonamide

Group 23

(1) 5-[6-(4-Iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-benzofuran-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzofuran-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-isobenzofuran-5-yl]-1,3,4- oxadiazol-2-ol

(6) 5-[6-(2-Chloro-4-iodo-phenylamino)-1-methyl-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

Group 24

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-1H-benzimidazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-benzo[b]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzo[b]thiophen-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-1,3-dihydro-benzo[c]thiophen-5-yl]-1,3,4-oxadiazol-2-ol

(6) 5-[6-(2-Chloro-4-iodo-phenylamino)-2-oxo-2,3-dihydro-1H-2$I>4_-2,1,3-benzothiadiazol-5-yl]-1,3,4-oxadiazol-2-ol

Group 25

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-1H-indol-6-yl]-1,3,4-oxadiazol-2-ol

(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4- oxadiazol-2-ol

(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

Group 26

(1) 5-[2-Amino-6-(4-iodo-2-methyl-phenylamino)-benzothiazol-5-yl]-1,3,4-oxadiazol-2-ol

(2) 5-[6-(4-Iodo-phenylamino)-1H-indol-5-yl]-1,3,4-oxadiazol-2-ol

(3) 5-[7-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoxazol-5-yl]-1,3,4-oxadiazol-2-ol

(4) 5-[5-(4-Iodo-phenylamino)-benzoxazol-6-yl]-1,3,4-oxadiazol-2-ol

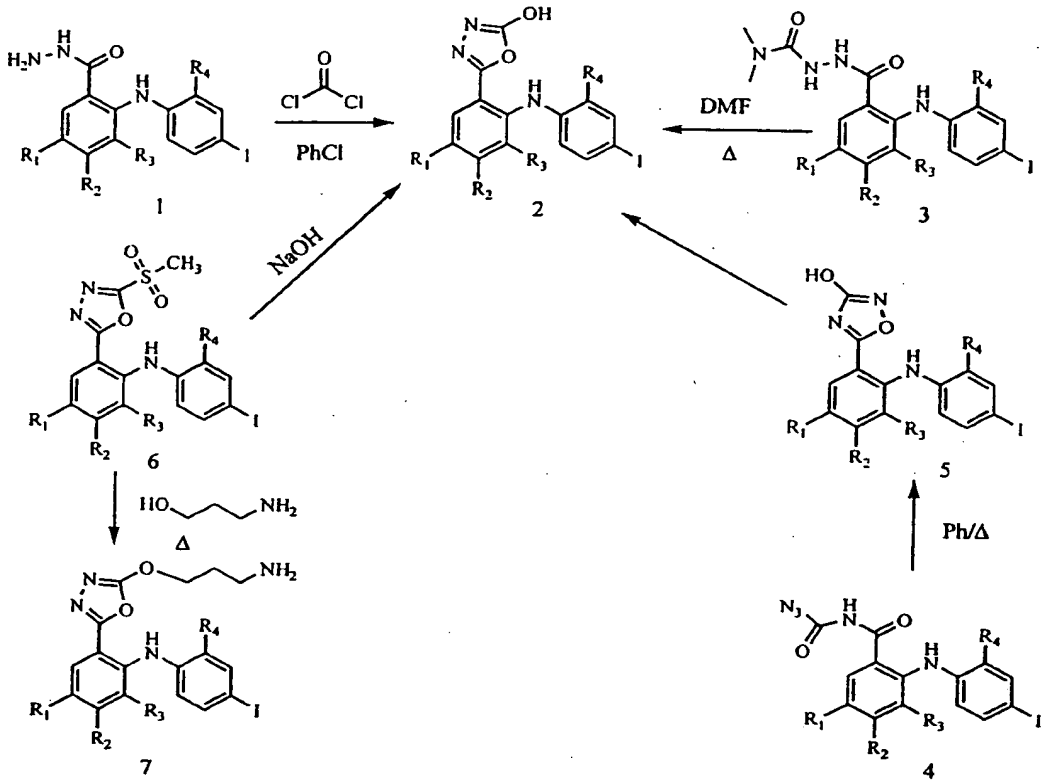
(5) 5-[6-(2-Chloro-4-iodo-phenylamino)-7-fluoro-2,3-dihydro-1H-isoindol-5-yl]-1,3,4- oxadiazol-2-ol

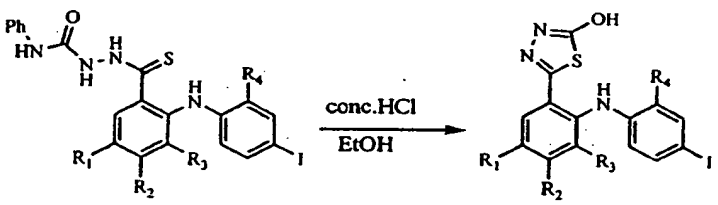
(6) 5-[5-(2-Chloro-4-iodo-phenylamino)-1H-indazol-6-yl]-1,3,4-oxadiazol-2-ol

C. Synthesis

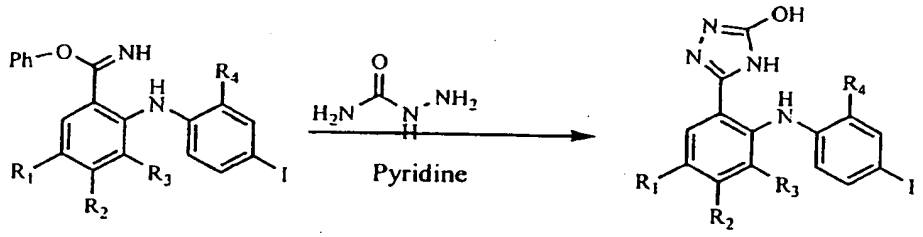
The disclosed compounds can be synthesized according to Schemes 1-25 or analogous variants thereof. These synthetic strategies are further exemplified in Examples 1-8 below. The solvent between compounds 4 and 5 in Scheme 1 is toluene (PhMe).

Scheme 1





Scheme 2



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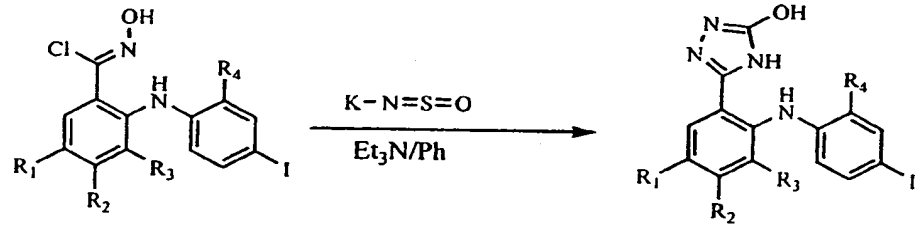

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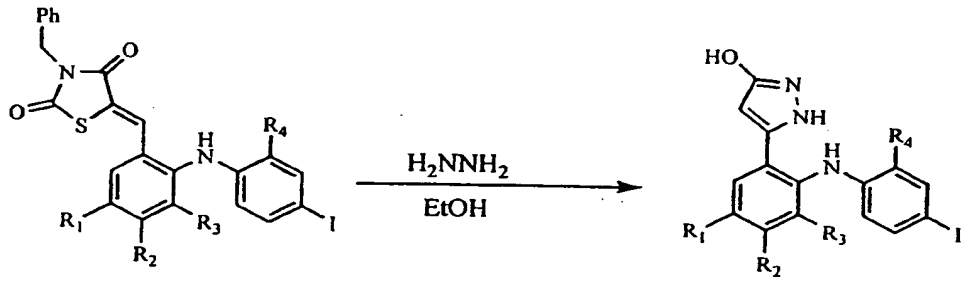

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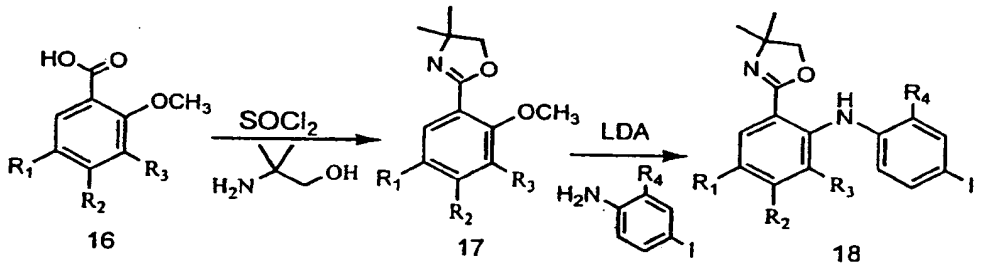
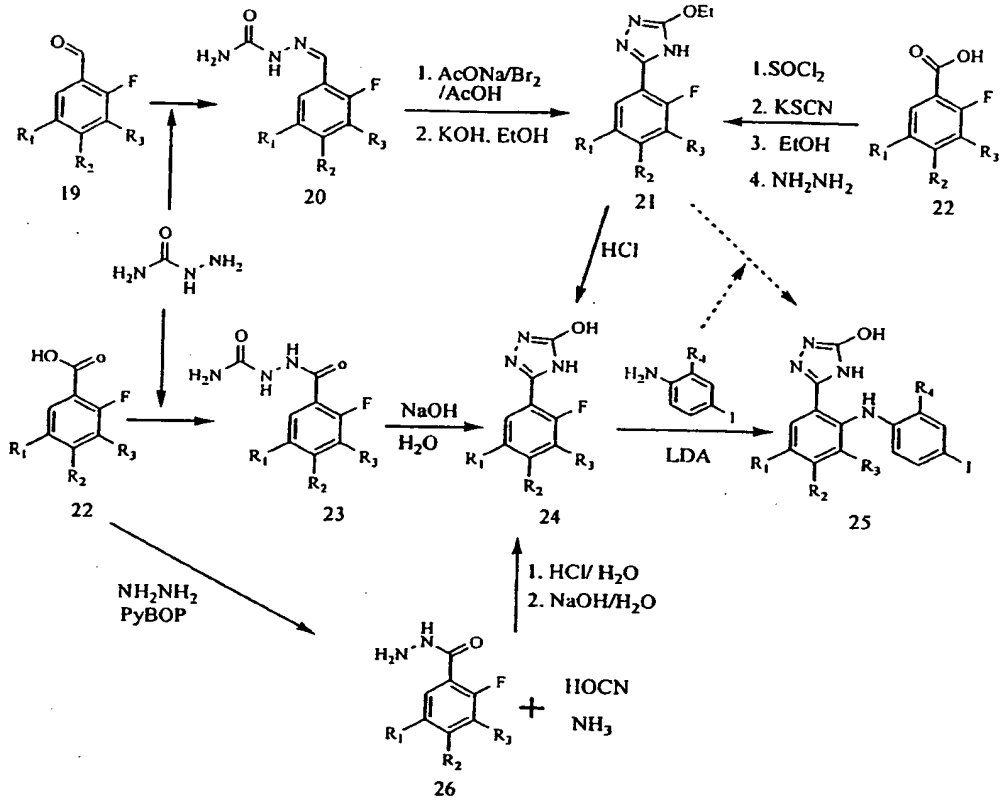
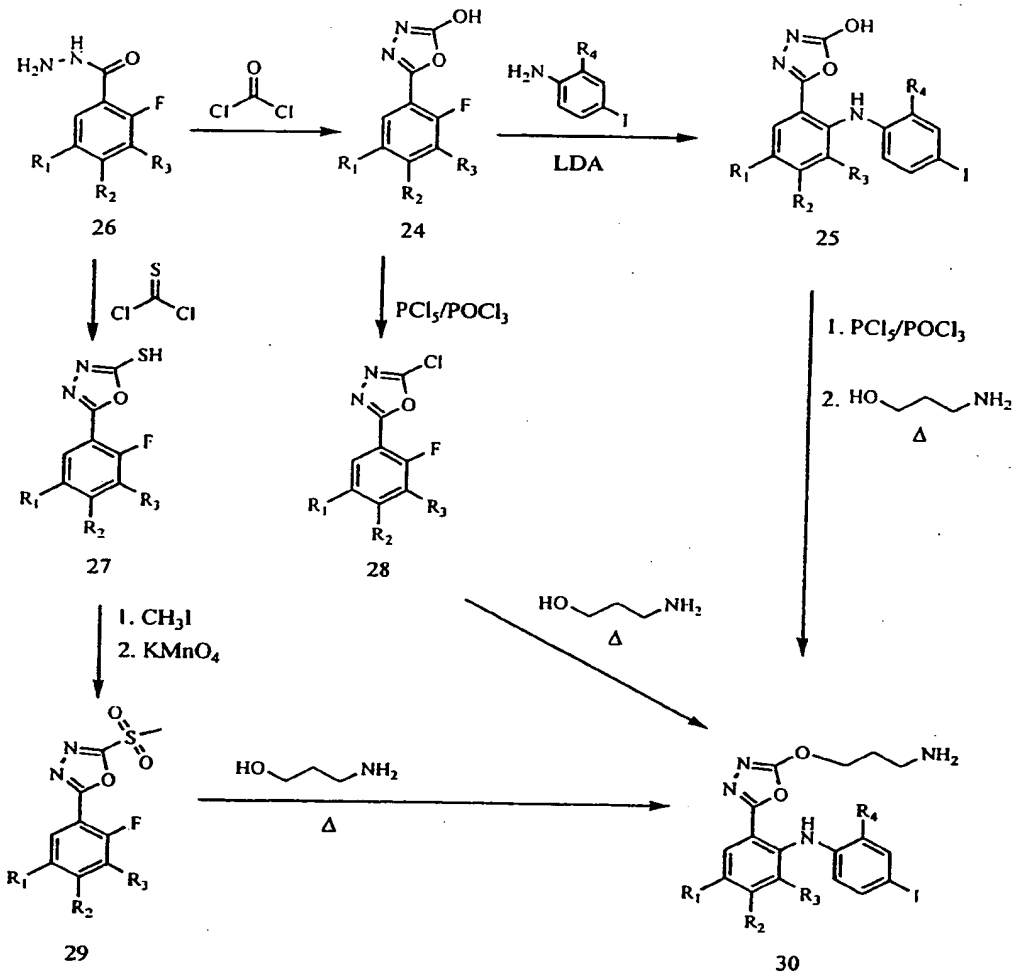


16 17 18

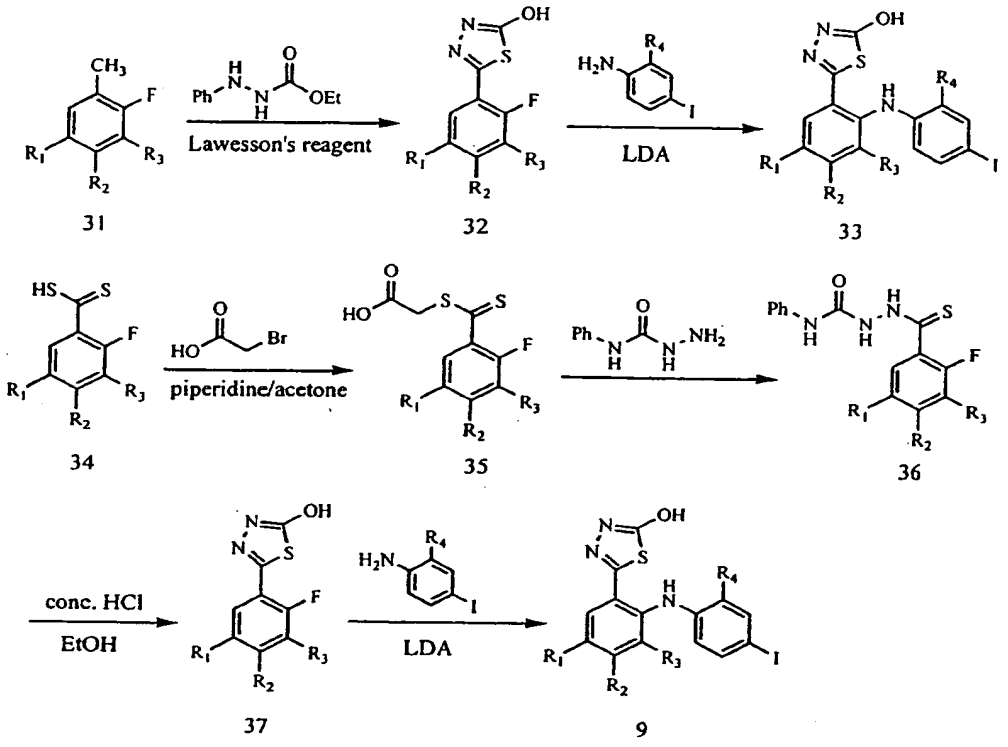
Scheme 3


1. AcONa/Br2 /AcOH
2. KOH. EtOH
1.SOCl2
2. KSCN
3. EtOH
4. NH2NH2
HCl
NaOH
H2O
LDA
NH2NH2
PyBOP
1. HCl/ H2O
2. NaOH/H2O
HOCN
NH3
19
20
21
22
22
23
24
25
26

Scheme 4



Scheme 5

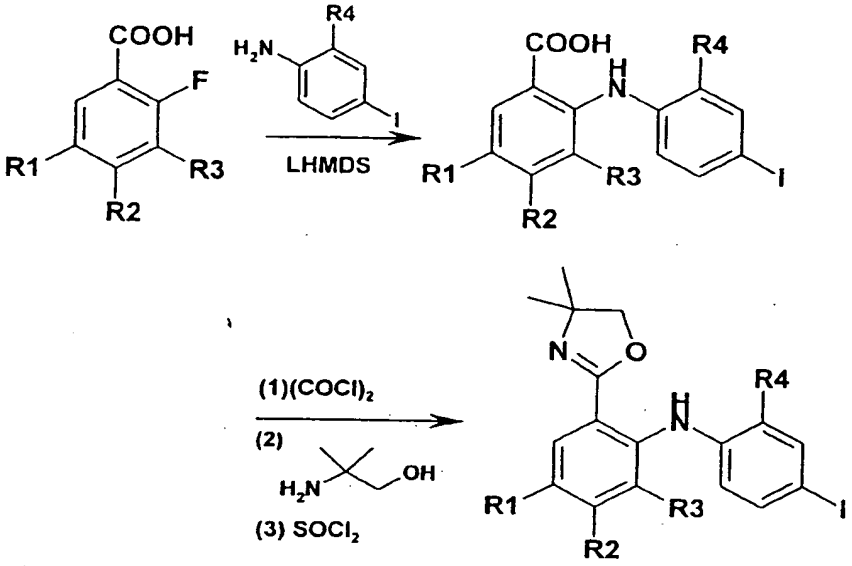


31 32 33

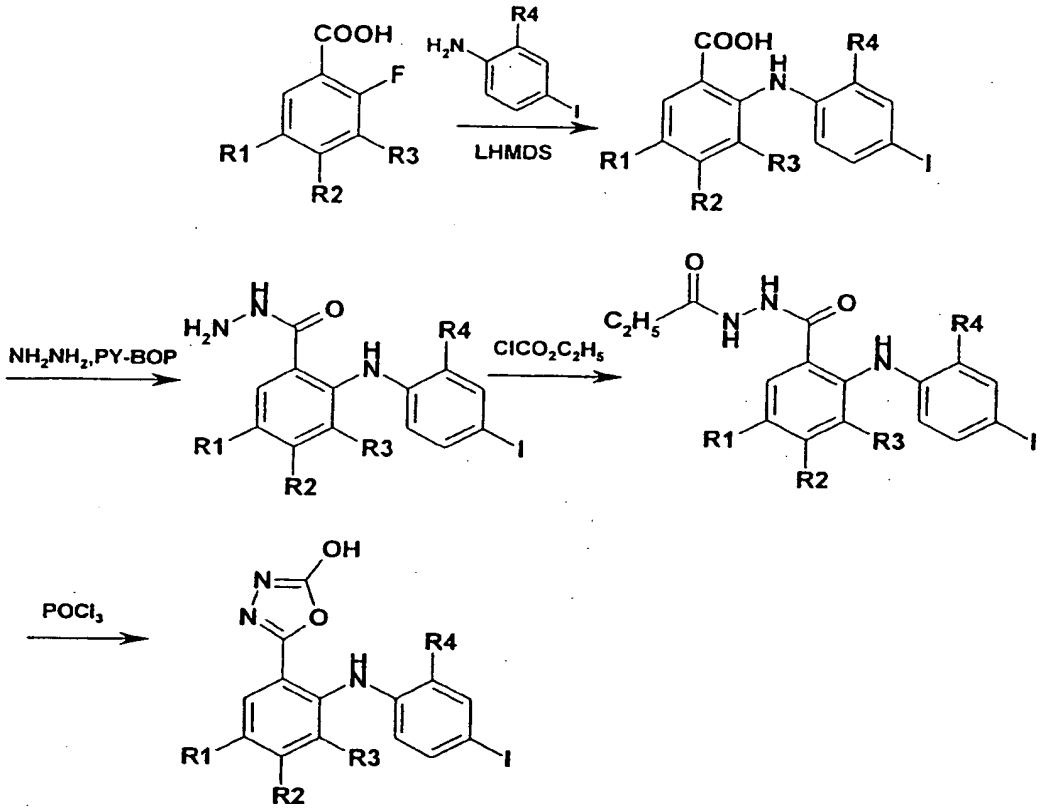
34 35 36

37 9

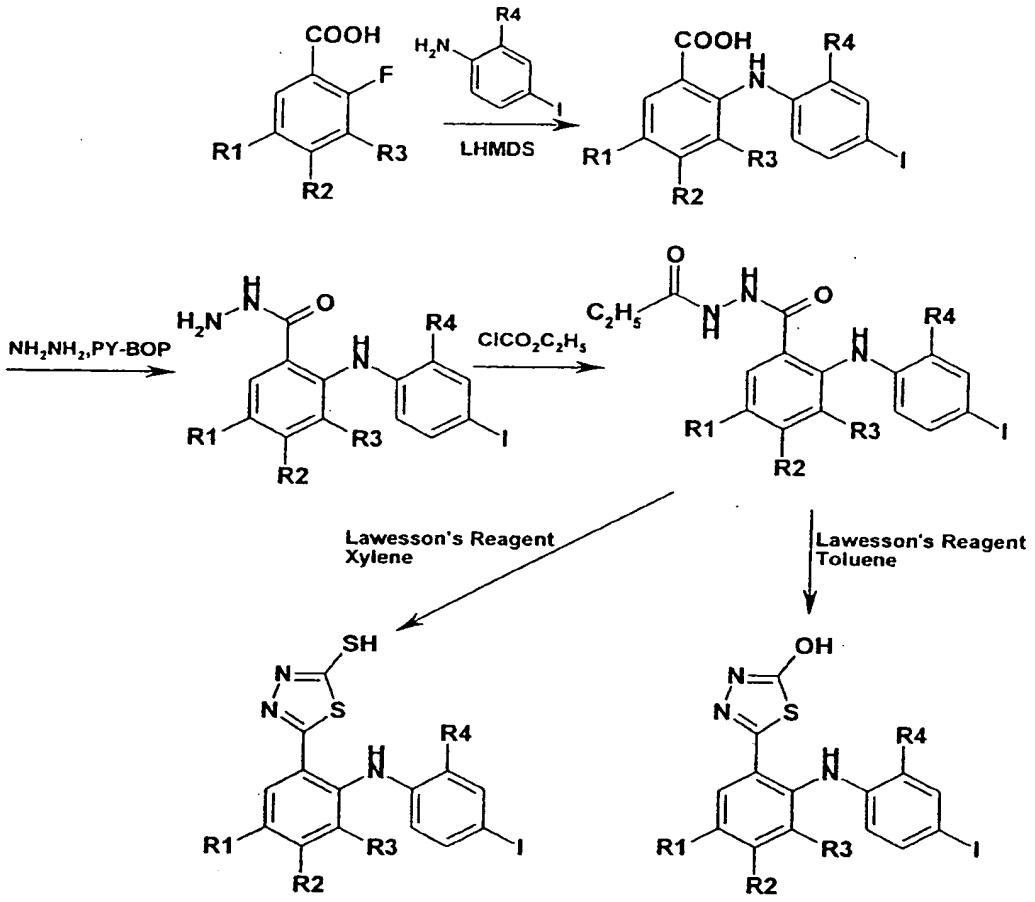
Scheme 6


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
H
N
R1
R3
I
R2
(1)(COCl)2
(2)
H2N
OH
(3) SOCl2
N
O
R4
H
N
R1
R3
I
R2

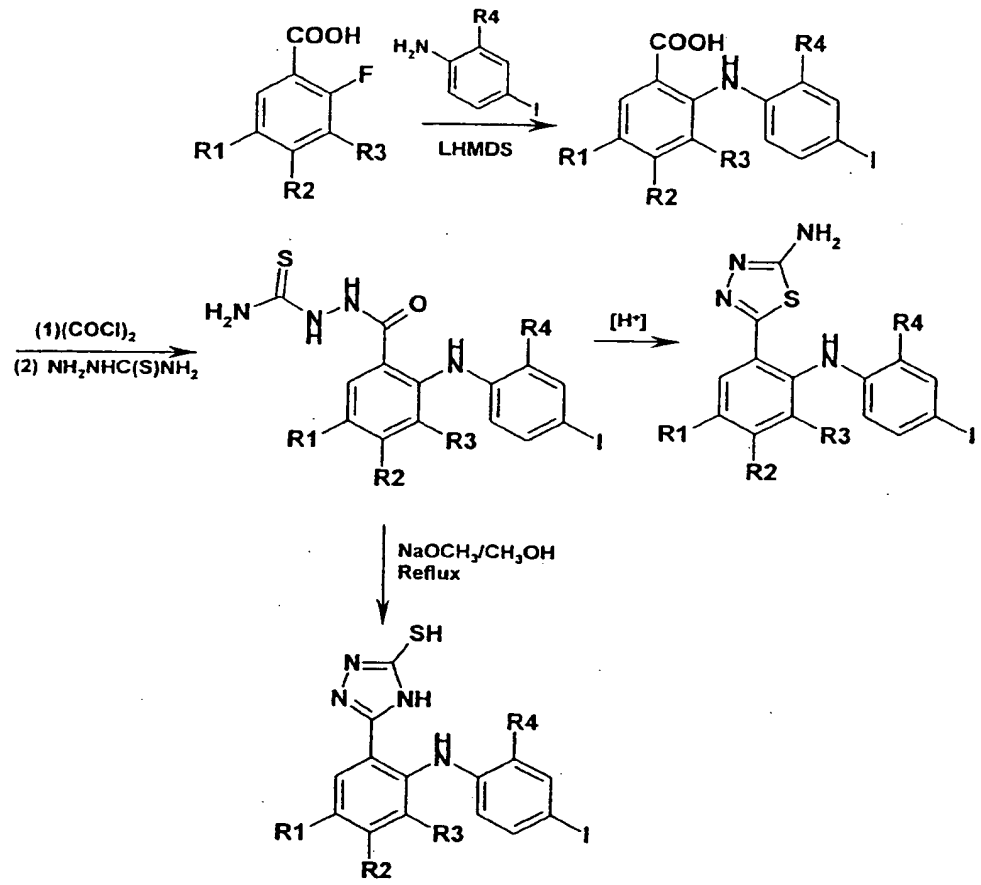
Scheme 7


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
NH2NH2,PY-BOP
ClCO2C2H5
C2H5
O
N
H
POCl3
OH

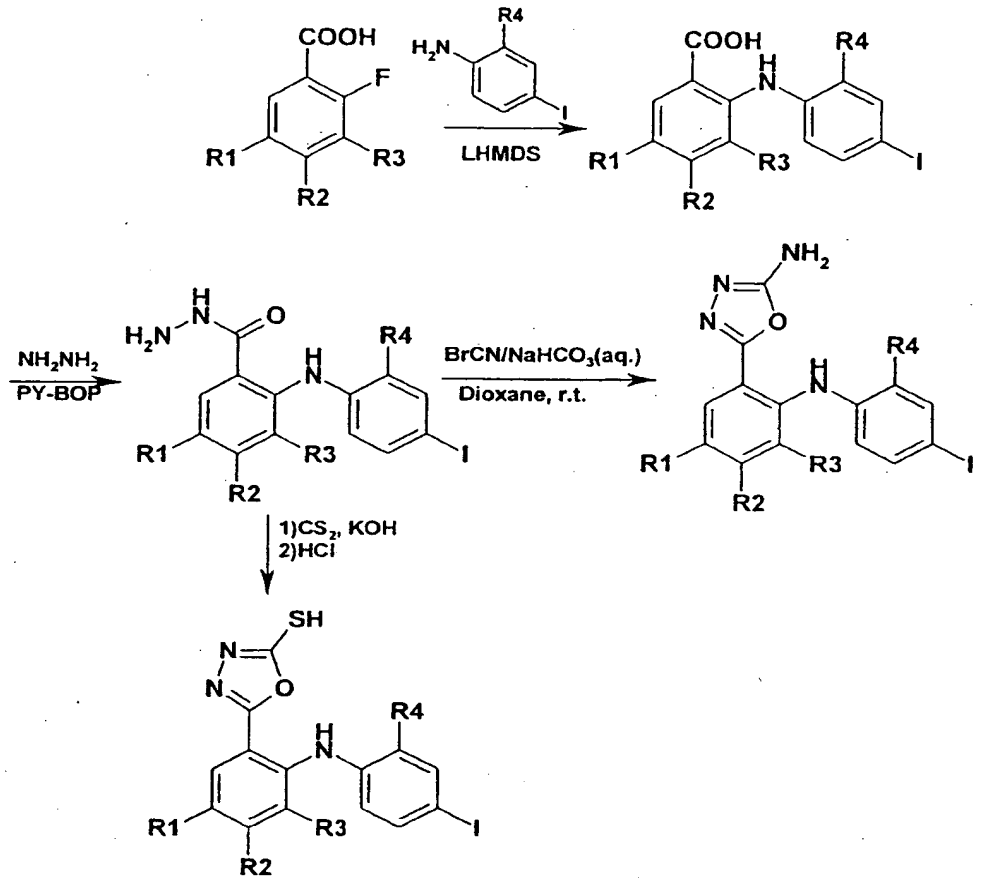
Scheme 8


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
NH_2NH_2,PY-BOP
H_2N
N
H
O
R4
N
H
R1
R3
R2
I
$ClCO_2C_2H_5$
C_2H_5
O
N
H
N
H
O
R4
N
H
R1
R3
R2
I
Lawesson's Reagent
Xylene
Lawesson's Reagent
Toluene
SH
N
N
S
R4
N
H
R1
R3
R2
I
OH
N
N
S
R4
N
H
R1
R3
R2
I

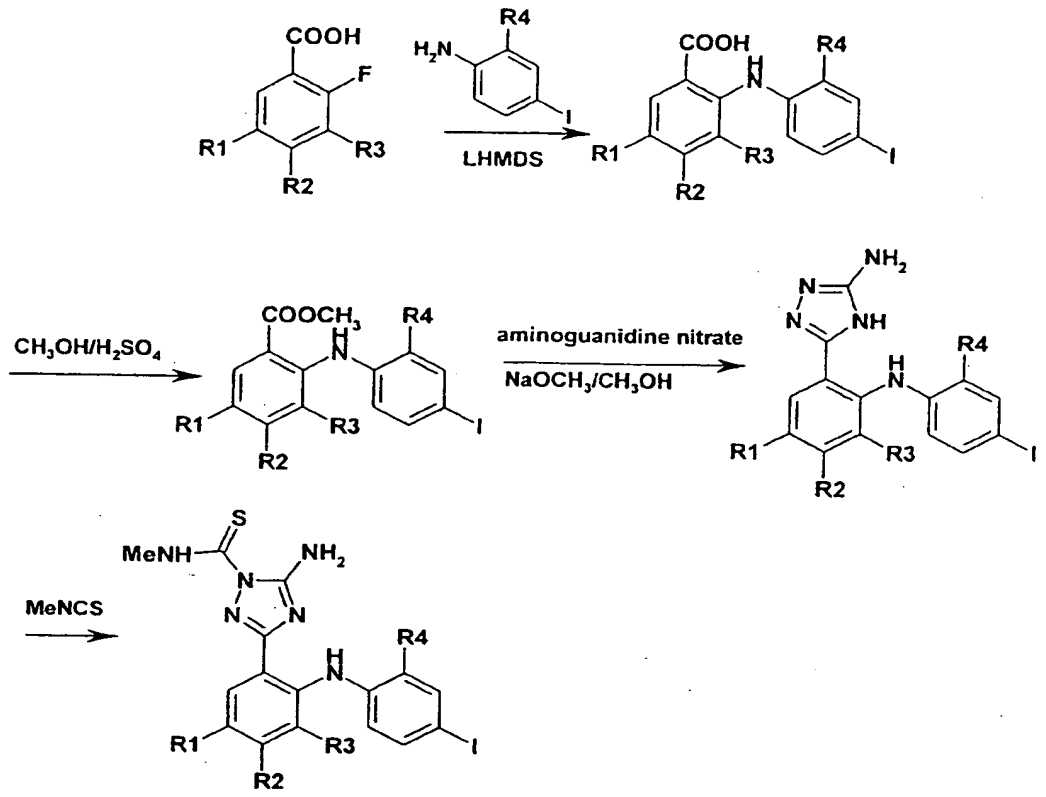
Scheme 9


COOH
F
R1
R3
R2
H2N
R4
I
LHMDS
COOH
N
(1)(COCl)2
(2) NH2NHC(S)NH2
S
H2N
O
[H+]
NH2
N
S
NaOCH3/CH3OH
Reflux
SH
NH

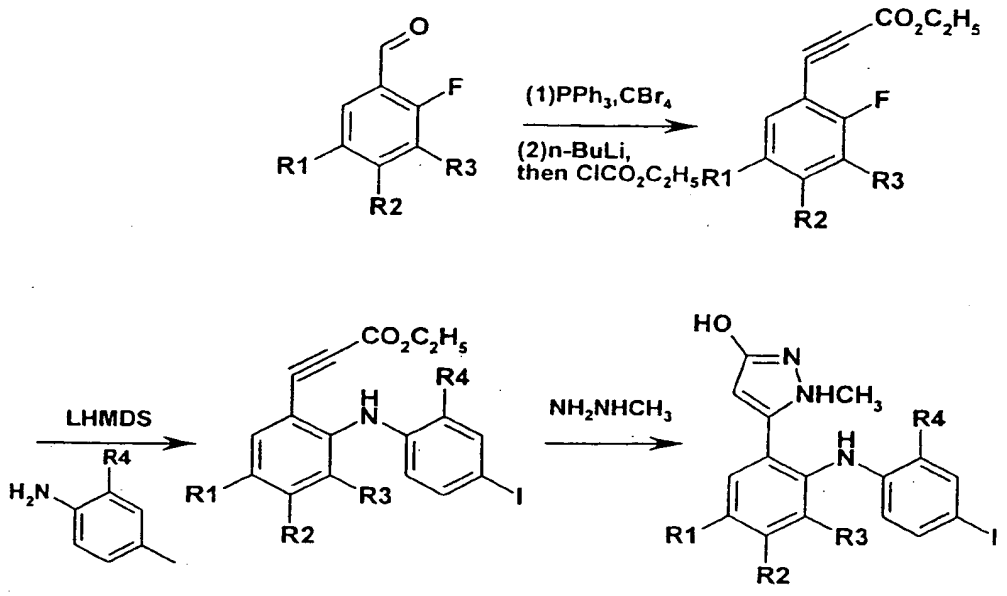
Scheme 10


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
NH_2NH_2
PY-BOP
H_2N
H
N
O
R4
H
N
R1
R3
R2
I
BrCN/$NaHCO_3$(aq.)
Dioxane, r.t.
NH_2
N
N
O
R4
H
N
R1
R3
R2
I
1)CS_2, KOH
2)HCl
SH
N
N
O
R4
H
N
R1
R3
R2
I

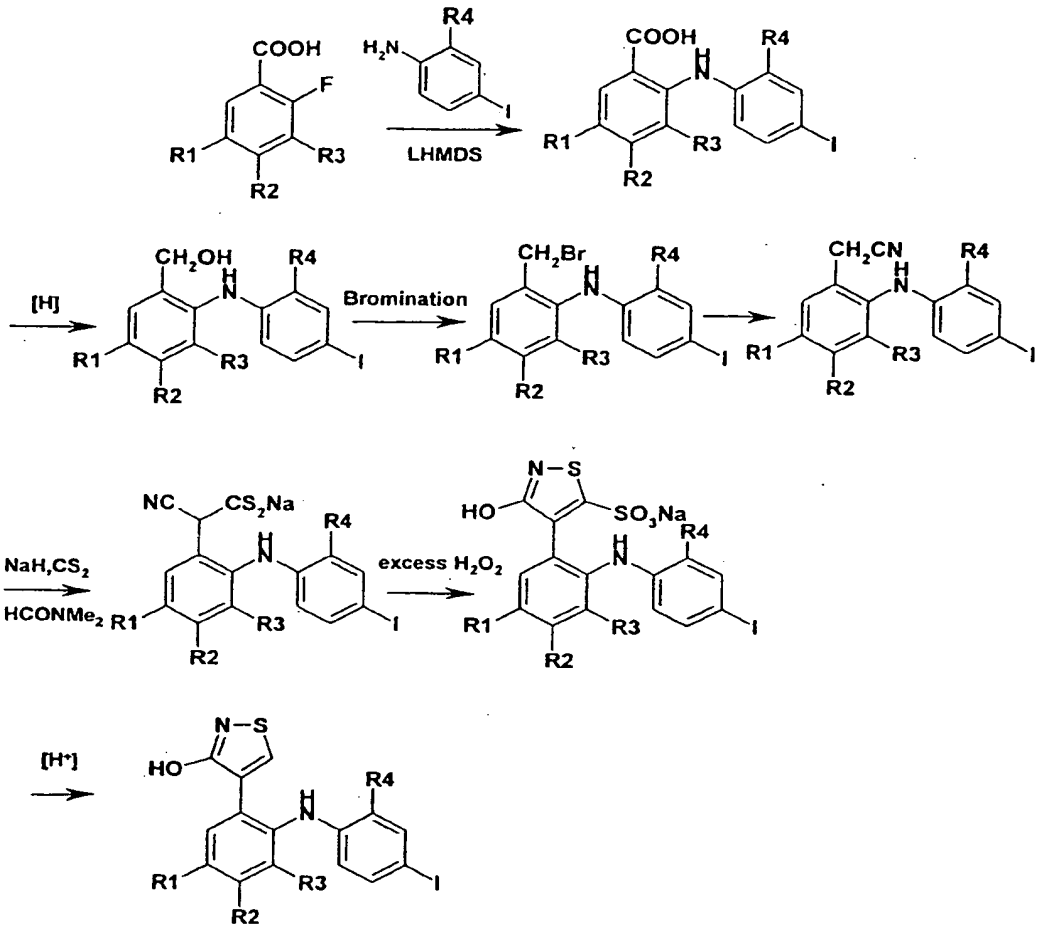
Scheme 11


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
H
N
R4
R1
R3
R2
I
CH_3OH/H_2SO_4
$COOCH_3$
H
N
R4
R1
R3
R2
I
aminoguanidine nitrate
$NaOCH_3/CH_3OH$
NH_2
N
N
NH
H
N
R4
R1
R3
R2
I
MeNCS
S
MeNH
NH_2
N
N
N
H
N
R4
R1
R3
R2
I

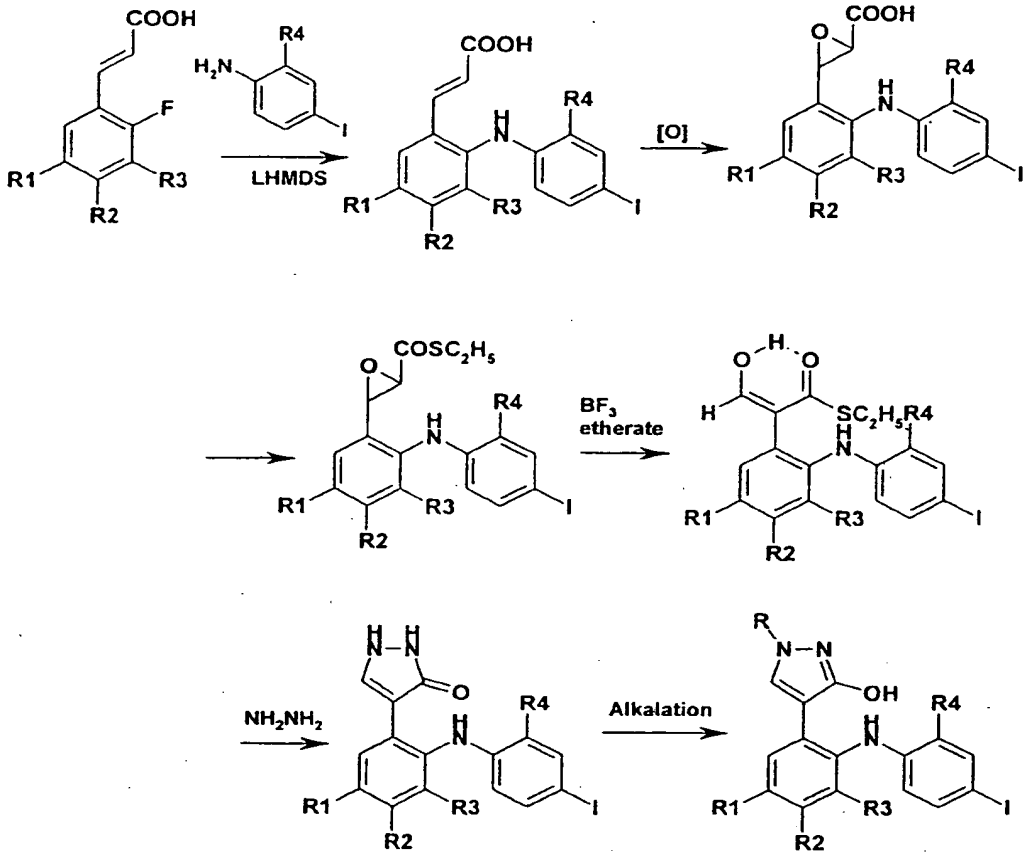
Scheme 12


O
F
R1
R3
R2
(1)PPh3,CBr4
(2)n-BuLi,
then ClCO2C2H5
CO2C2H5
F
R1
R3
R2
LHMDS
R4
H2N
CO2C2H5
R4
H
N
R1
R3
R2
I
NH2NHCH3
HO
N
NHCH3
R4
H
N
R1
R3
R2
I

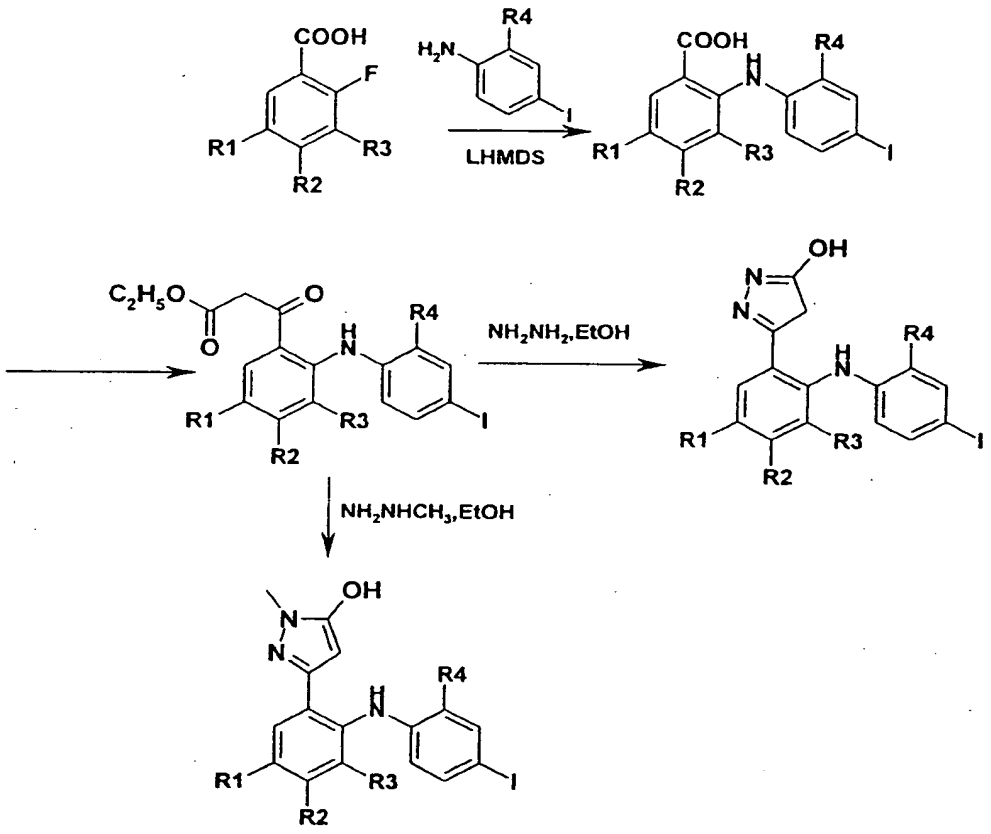
Scheme 13


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
[H]
CH_2OH
R4
H
N
R1
R3
R2
I
Bromination
CH_2Br
R4
H
N
R1
R3
R2
I
CH_2CN
R4
H
N
R1
R3
R2
I
NaH,CS_2
$HCONMe_2$
NC
CS_2Na
R4
H
N
R1
R3
R2
I
excess H_2O_2
N–S
HO
SO_3Na
R4
H
N
R1
R3
R2
I
[H+]
N–S
HO
R4
H
N
R1
R3
R2
I

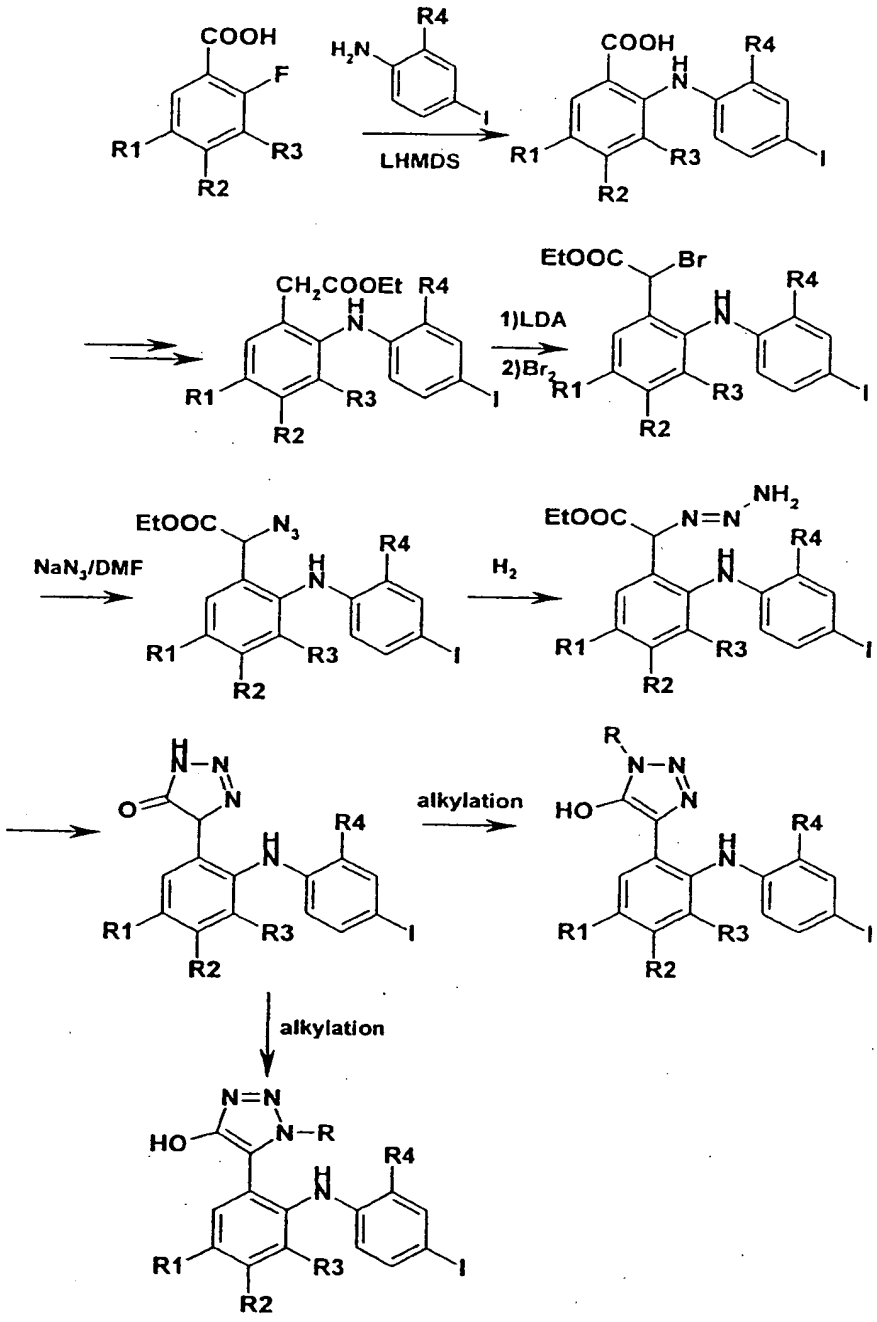
Scheme 14


COOH
F
R1
R3
R2
H2N
R4
I
LHMDS
COOH
R4
N
H
R1
R3
R2
I
[O]
COOH
O
R4
N
H
R1
R3
R2
I
COSC2H5
O
R4
N
H
R1
R3
R2
I
BF3
etherate
O
H
O
H
O
SC2H5R4
N
H
R1
R3
R2
I
NH2NH2
N–N
H
O
R4
N
H
R1
R3
R2
I
Alkalation
R
N–N
OH
R4
N
H
R1
R3
R2
I

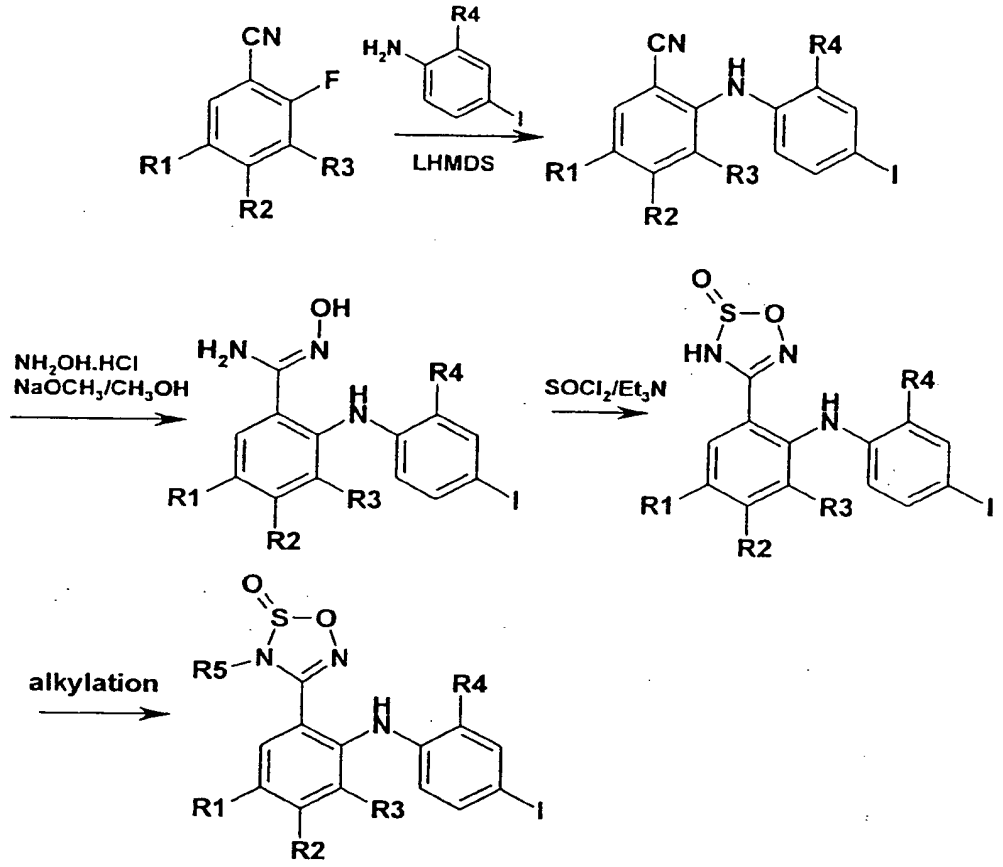
Scheme 15


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
C_2H_5O
O
O
R4
H
N
R1
R3
R2
I
NH_2NH_2,EtOH
OH
N
N
R4
H
N
R1
R3
R2
I
NH_2NHCH_3,EtOH
OH
N
N
R4
H
N
R1
R3
R2
I

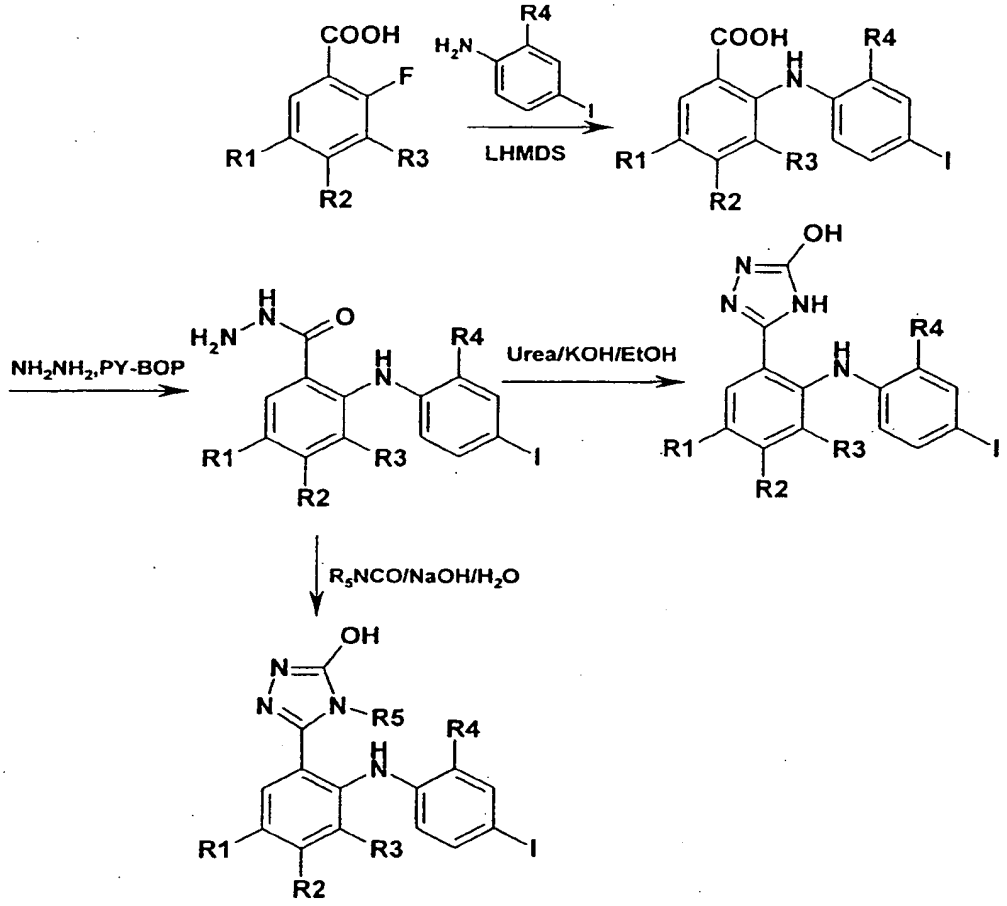
Scheme 16


COOH
F
R1
R3
R2
H2N
R4
I
LHMDS
N
H
CH2COOEt
EtOOC
Br
1)LDA
2)Br2
NaN3/DMF
N3
H2
NH2
N=N
alkylation
HO
R

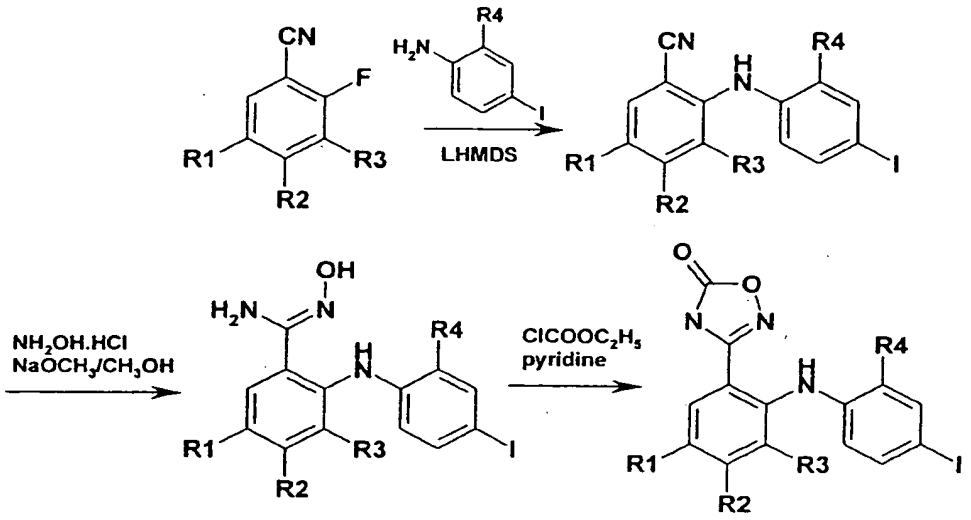
Scheme 17


CN
F
R1
R3
R2
R4
H2N
I
LHMDS
CN
R4
H
N
R1
R3
R2
I
NH2OH.HCl
NaOCH3/CH3OH
OH
H2N
N
R4
H
N
R1
R3
R2
I
SOCl2/Et3N
O
S
O
HN
N
R4
H
N
R1
R3
R2
I
alkylation
O
S
O
R5
N
N
R4
H
N
R1
R3
R2
I

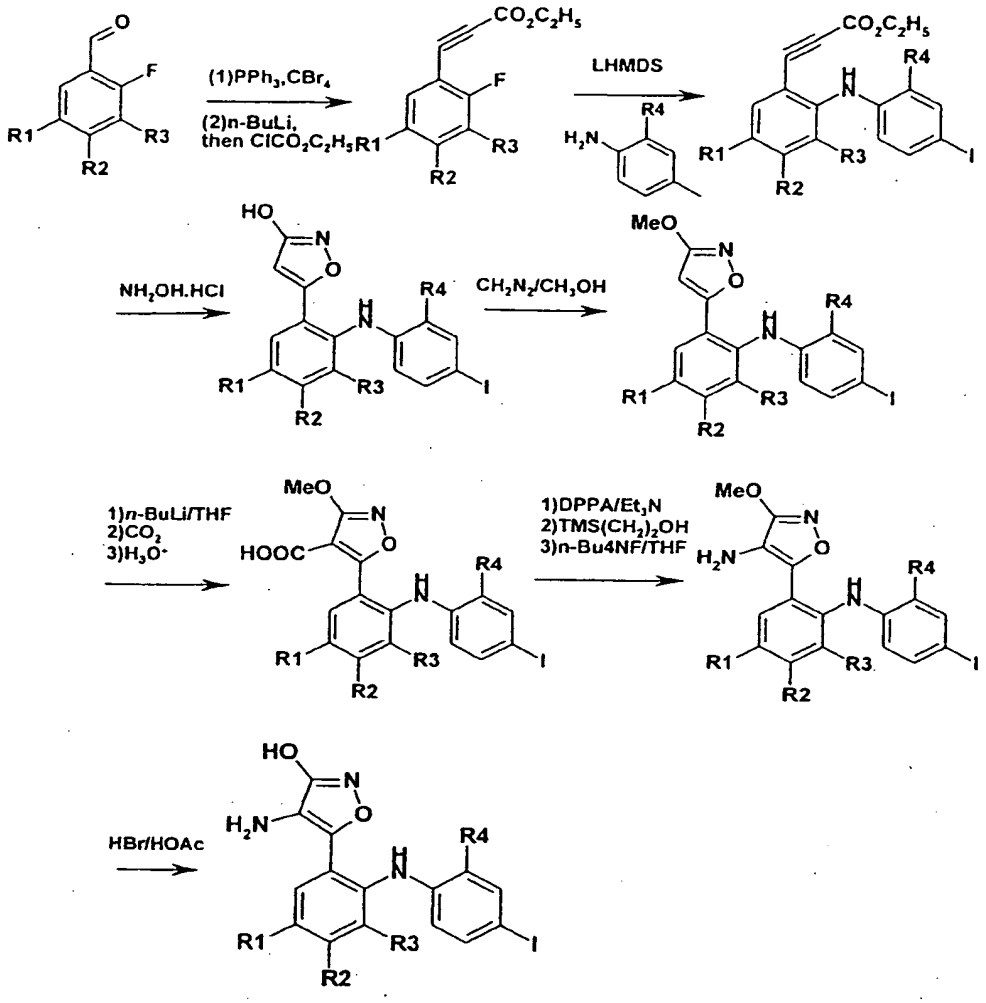
Scheme 18


COOH
F
R1
R3
R2
R4
H2N
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
NH2NH2,PY-BOP
H2N
N
H
O
R4
H
N
R1
R3
R2
I
Urea/KOH/EtOH
OH
N
N
NH
R4
H
N
R1
R3
R2
I
R5NCO/NaOH/H2O
OH
N
N
N
R5
R4
H
N
R1
R3
R2
I

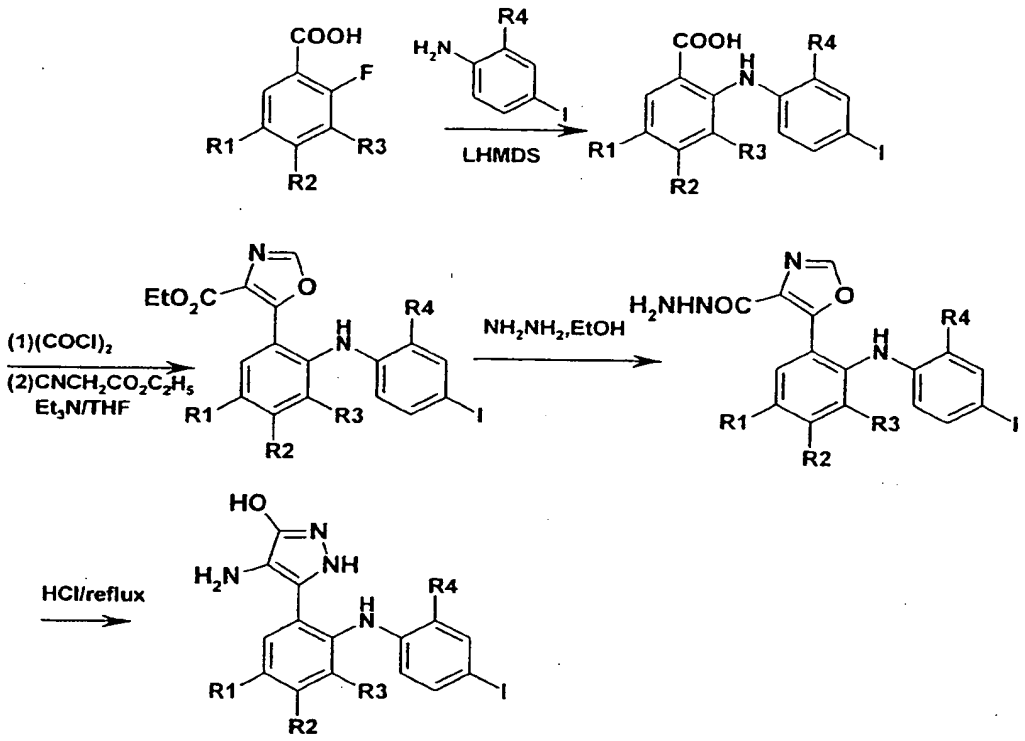
Scheme 19


CN
F
R1
R3
R2
R4
H2N
I
LHMDS
CN
H
N
R4
R1
R3
I
R2
NH2OH.HCl
NaOCH3/CH3OH
OH
H2N
N
H
N
R4
R1
R3
R2
I
ClCOOC2H5
pyridine
O
O
N
N
H
N
R4
R1
R3
R2
I

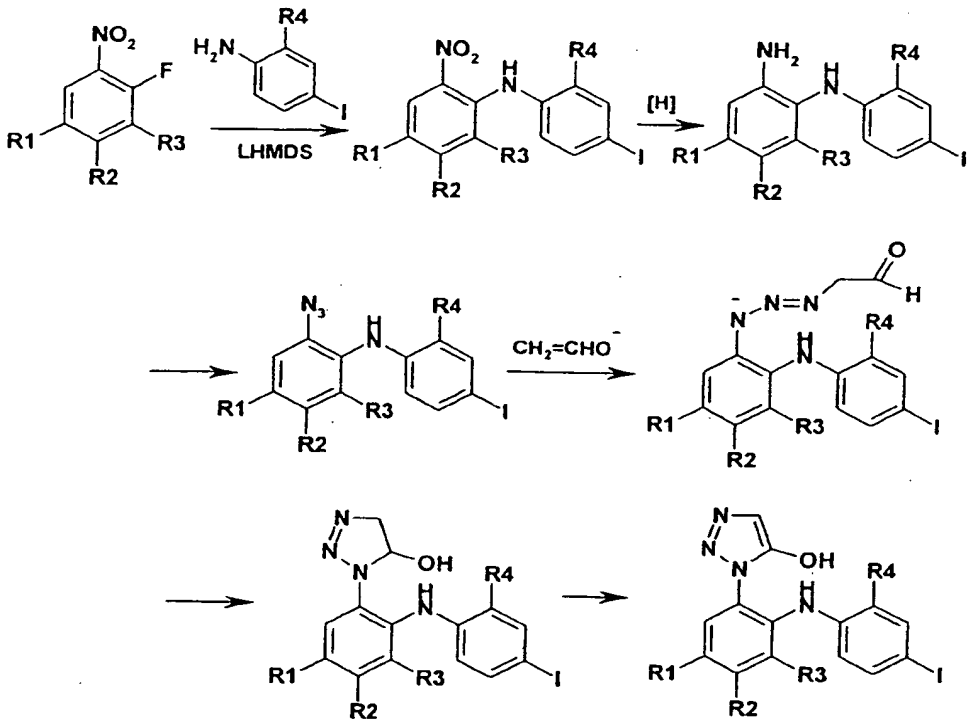
Scheme 20


(1)PPh3,CBr4
(2)n-BuLi,
then ClCO2C2H5
LHMDS
NH2OH.HCl
CH2N2/CH3OH
1)n-BuLi/THF
2)CO2
3)H3O+
1)DPPA/Et3N
2)TMS(CH2)2OH
3)n-Bu4NF/THF
HBr/HOAc

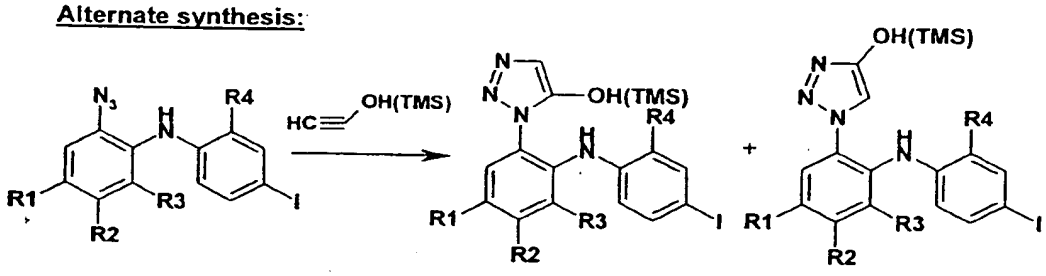
Scheme 21


COOH
F
R1
R3
R2
R4
H_2N
I
LHMDS
N
H
O
EtO_2C
(1)$(COCl)_2$
(2)$CNCH_2CO_2C_2H_5$
Et_3N/THF
NH_2NH_2,EtOH
H_2NHNOC
HO
H_2N
NH
HCl/reflux

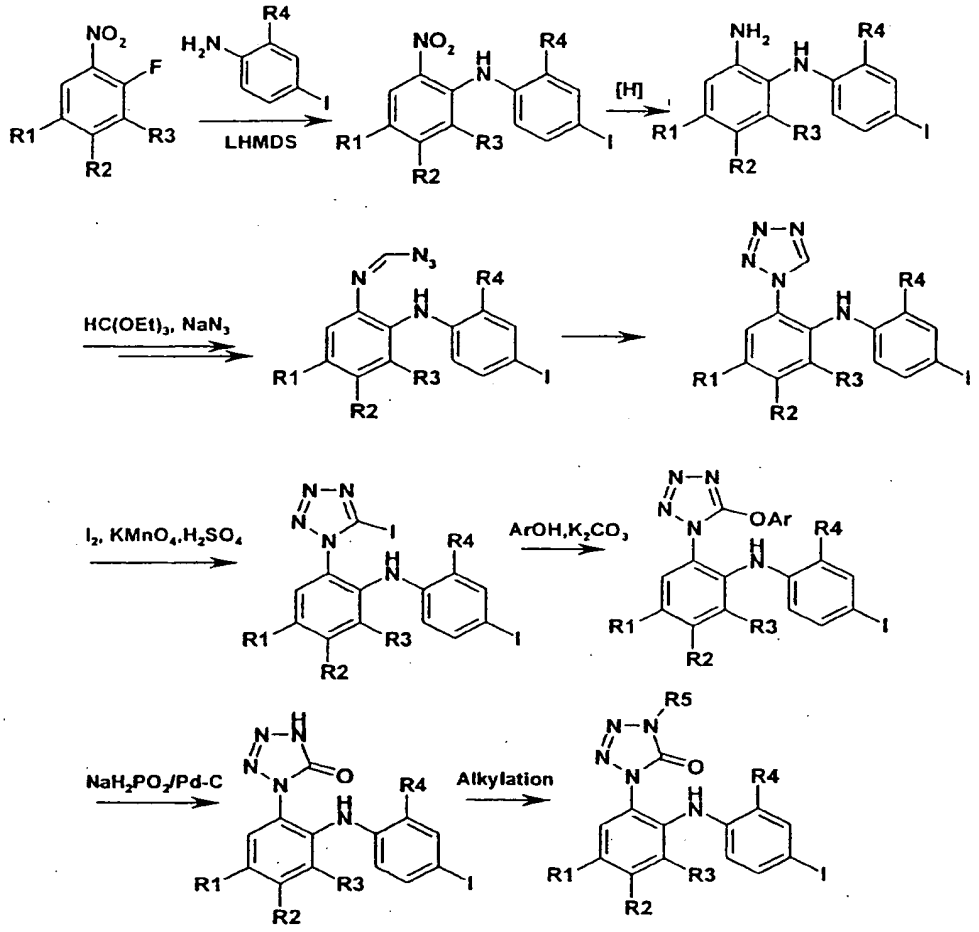
Scheme 22



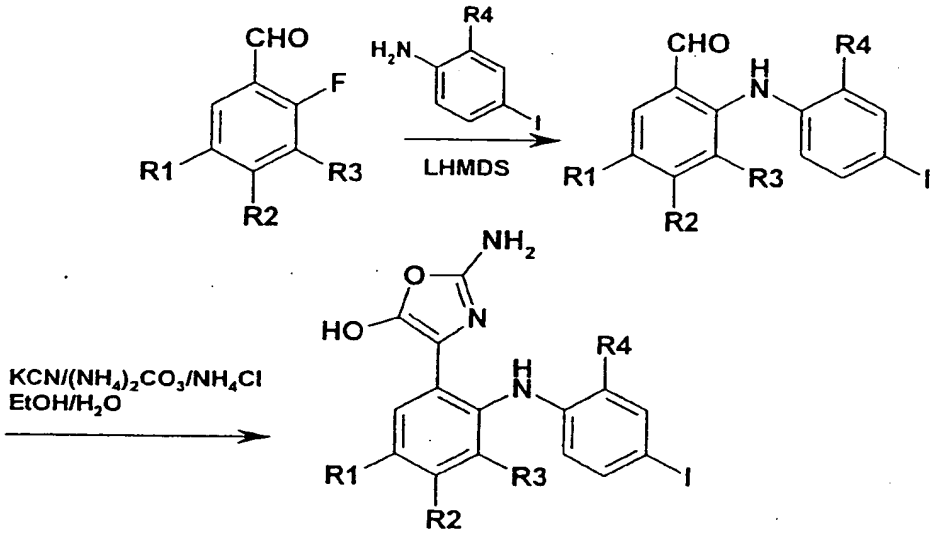
Alternate synthesis:



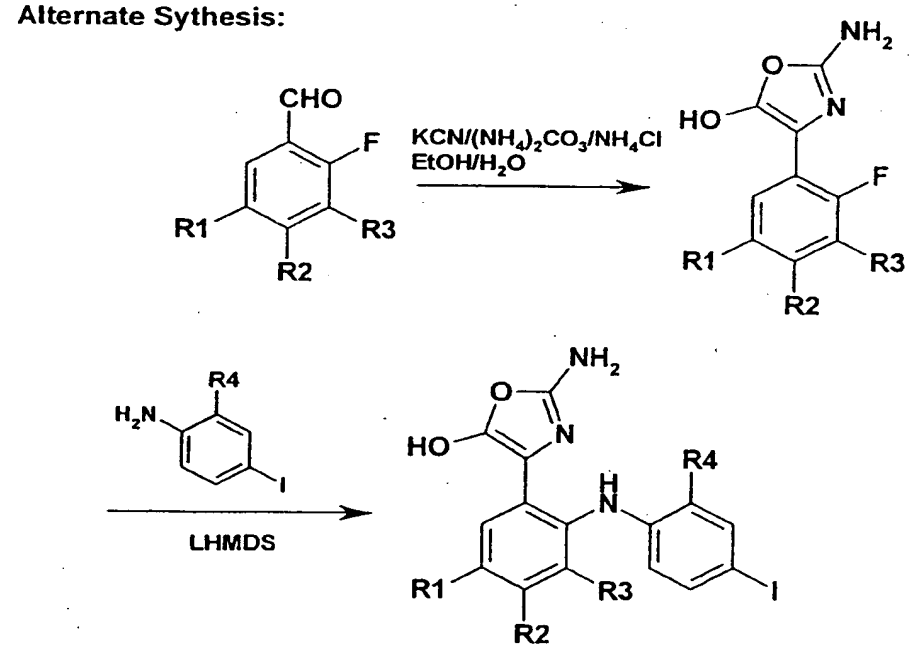
Scheme 23


LHMDS
[H]
HC(OEt)3, NaN3
I2, KMnO4,H2SO4
ArOH,K2CO3
NaH2PO2/Pd-C
Alkylation

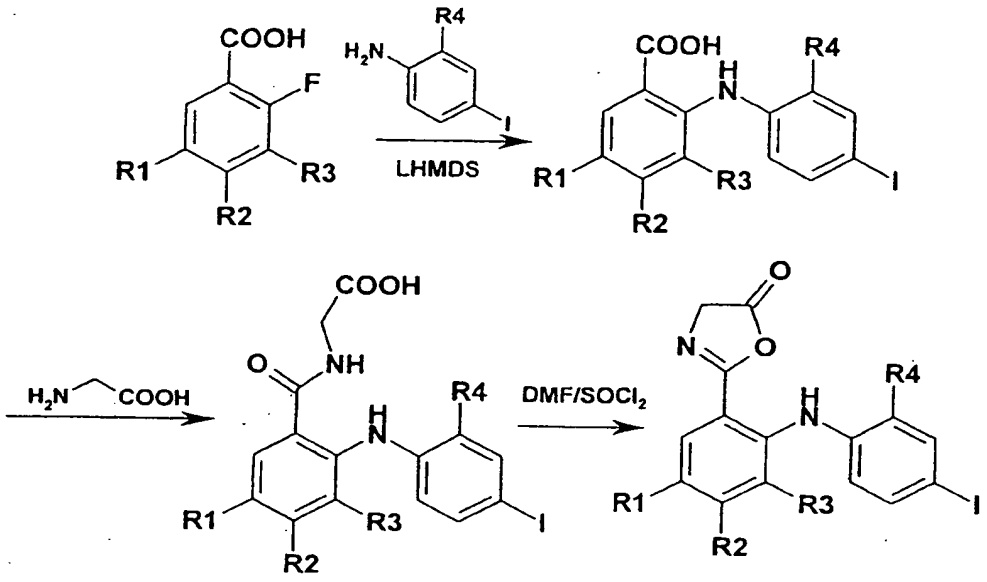
Scheme 24



Alternate Sythesis:



Scheme 25


COOH
F
R1
R3
R2
H2N
R4
I
LHMDS
COOH
R4
H
N
R1
R3
R2
I
H2N
COOH
COOH
O
NH
R4
H
N
R1
R3
R2
I
DMF/SOCl2
O
N
O
O
R4
H
N
R1
R3
R2
I

D. Uses

The disclosed compositions are useful as both prophylactic and therapeutic treatments for diseases or conditions as provided in the Summary section, as well as diseases or conditions modulated by the MEK cascade. Examples include stroke, heart failure, osteoarthritis, rheumatoid arthritis, organ transplant rejection, and a variety of tumors such as ovarian, lung, pancreatic, brain, prostatic, and colorectal.

1. Dosages

Those skilled in the art will be able to determine, according to known methods, the appropriate dosage for a patient, taking into account factors such as age, weight, general health, the type of pain requiring treatment, and the presence of other medications. In general, an effective amount will be between 0.1 and 1000 mg/kg per day, preferably between 1 and 300 mg/kg body weight, and daily dosages will be between 10 and 5000 mg for an adult subject of normal weight. Commercially available capsules or other formulations (such as liquids and film-coated tablets) of 100 mg, 200 mg, 300 mg, or 400 mg can be administered according to the disclosed methods.

2. Formulations

Dosage unit forms include tablets, capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers adapted for subdivision into individual doses. Dosage unit forms can also be adapted for various methods of administration, including controlled release formulations, such as subcutaneous implants. Administration methods include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical, local (drops, powders, ointments, gels, or cream), and by inhalation (a buccal or nasal spray).

Parenteral formulations include pharmaceutically acceptable aqueous or nonaqueous solutions, dispersion, suspensions, emulsions, and sterile powders for the preparation thereof. Examples of carriers include water, ethanol, polyols (propylene glycol, polyethylene glycol), vegetable oils, and injectable organic esters such as ethyl oleate. Fluidity can be maintained by the use of a coating

such as lecithin, a surfactant, or maintaining appropriate particle size. Carriers for solid dosage forms include (a) fillers or extenders, (b) binders, (c) humectants, (d) disintegrating agents, (e) solution retarders, (f) absorption acccelerators, (g) adsorbants, (h) lubricants, (i) buffering agents, and (j) propellants.

Compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents; antimicrobial agents such as parabens, chlorobutanol, phenol, and sorbic acid; isotonic agents such as a sugar or sodium chloride; absorption-prolonging agents such as aluminum monostearate and gelatin; and absorption-enhancing agents.

3. Related compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms.

Pharmaceutically acceptable salts, esters, and amides include carboxylate salts (e.g., C_{1-8} alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic), amino acid addition salts, esters, and amides which are within a reasonable benefit/risk ratio, pharmacologically effective, and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C_{1-6} alkyl amines and secondary di (C_{1-6} alkyl) amines. Secondary amines include 5- or 6-membered

heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C_{1-3} alkyl primary amines, and di (C_{1-2} alkyl)amines. Representative pharmaceutically acceptable esters of the invention include C_{1-7} alkyl, C_{5-7} cycloalkyl, phenyl, and phenyl(C_{1-6})alkyl esters. Preferred esters include methyl esters.

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. Some of these masked or protected compounds are pharmaceutically acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

HYDROXYL PROTECTING GROUPS

Hydroxyl protecting groups include: ethers, esters, and protection for 1,2- and 1,3-diols. The ether protecting groups include: methyl, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, silyl ethers and conversion of silyl ethers to other functional groups.

Substituted Methyl Ethers

Substituted methyl ethers include: methoxymethyl, methylthiomethyl, *t*-utylthiomethyl, (phenyldimethylsilyl) methoxymethyl, benzyloxymethyl, *p*-ethoxybenzyloxymethyl, (4-methoxyphenoxy) methyl, guaiacolmethyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloro- ethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydro-pyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothio-pyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-ethanobenzofuran-2-yl.

Substituted Ethyl Ethers

Substituted ethyl ethers include: 1-ethoxyethyl, 1-(2,chloroethoxy)ethyl,

1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, and benzyl.

Substituted Benzyl Ethers

Substituted benzyl ethers include: *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenyl-methyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri-(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl) methyl, 4,4',4"tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)-methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl) xanthenyl, 9-(9-phenyl-10-oxo) anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl *S,S*-dioxido.

Silyl Ethers

Silyl ethers include: trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

ESTERS

Esters protecting groups include: esters, carbonates, assisted cleavage, miscellaneous esters, and sulfonates.

Esters

Examples of protective esters include: formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio) pentanoate, pivaloate, adamantoate,crotonate,4-

methoxycrotonate, benzoate, *p*-phenylbenzoate, and 2,4,6-trimethylbenzoate (mesitoate).

Carbonates

Carbonates include: methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl) ethyl, 2-(triphenylphosphonio) ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

Examples of assisted cleavage protecting groups include: 2-iodobenzoate, 4-azido-butyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl) benzoate, 2-formylbenzene-sulfonate, 2-(methylthiomethoxy) ethyl carbonate, 4-(methylthiomethoxymethyl) benzoate, and 2-(methylthiomethoxymethyl) benzoate.

Miscellaneous Esters

In addition to the above classes, miscellaneous esters include: 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl) phenoxyacetate, 2,4-bis(1,1-dimethylpropyl) phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate (tigloate), *o*-(methoxycarbonyl) benzoate, *p*-P-benzoate, α-naphthoate, nitrate, alkyl *N,N,N' N'*-tetramethylphosphorodiamidate, *N*-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

Sulfonates

Protective sulfates includes: sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

PROTECTION FOR 1,2- AND 1,3-DIOLS

The protection for 1,2 and 1,3-diols group includes: cyclic acetals and ketals, cyclic ortho esters, and silyl derivatives.

Cyclic Acetals and Ketals

Cyclic acetals and ketals include: methylene, ethylidene, 1-*t*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl) ethylidene, 2,2,2-trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

Cyclic Ortho Esters

Cyclic ortho esters include: methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidine, 1,2-dimethoxyethylidene, α-methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative, α-(*N,N*-dimethylamino) benzylidene derivative, and 2-oxacyclopentylidene.

PROTECTION FOR THE CARBOXYL GROUP

ESTERS

Ester protecting groups include: esters, substituted methyl esters, 2-substituted ethyl esters, substituted benzyl esters, silyl esters, activated esters, miscellaneous derivatives, and stannyl esters.

Substituted Methyl Esters

Substituted methyl esters include: 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxy-methyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl, α-methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and *N*-phthalimidomethyl.

2-Substituted Ethyl Esters

2-Substituted ethyl esters include: 2,2,2-trichloroethyl, 2-haloethyl, |-chloroalkyl, 2-(trimethylsily)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2(*p*-nitrophenylsulfenyl)-ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2′-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl,

allyl, 3-buten-1-yl, 4-(trimethylsily)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, phenyl, *p*-(methylmercapto)-phenyl, and benzyl.

Substituted Benzyl Esters

Substituted benzyl esters include: triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzosuberyl, 1-pyrenylmethyl,2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, and 4-P-benzyl.

Silyl Esters

Silyl esters include: trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di- *t*-butylmethylsilyl.

Miscellaneous Derivatives

Miscellaneous derivatives includes: oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group, and pentaaminocobalt(III) complex.

Stannyl Esters

Examples of stannyl esters include: triethylstannyl and tri-*n*-butylstannyl.

AMIDES AND HYDRAZIDES

Amides include: *N,N* –dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides. Hydrazides include: *N*-phenyl, *N,N'*-diisopropyl and other dialkyl hydrazides.

PROTECTION FOR THE AMINO GROUP

CARBAMATES

Carbamates include: carbamates, substituted ethyl, assisted cleavage, photolytic cleavage, urea-type derivatives, and miscellaneous carbamates.

Carbamates

Carbamates include: methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydro- thioxanthyl)]methyl, and 4-methoxyphenacyl.

Substituted Ethyl

Substituted ethyl protective groups include: 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N*,*N*-icyclohexylcarboxamido)- ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, connamyl, 4-nitrocinnamyl, quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl.

Assisted Cleavage

Protection via assisted cleavage includes: 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethyl-thiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolyl-methyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

Photolytic cleavage methods use groups such as: *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

Urea-Type Derivatives

Examples of of urea-type derivatives include: phenothiazinyl-(10)-carbonyl derivative, *N'*-p-toluenesulfonylaminocarbonyl, and *N'*-phenylaminothiocarbonyl.

Miscellaneous Carbamates

In addition to the above, miscellaneous carbamates include: *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxy-benzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethyl-carboxamido)-benzyl, 1,1-dimethyl-3(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethyl-propynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*(*p'*-methoxyphenyl-azo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropyl-methyl, 1-methyl-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1(*p*-henylazophenyl)-ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium) benzyl, and 2,4,6-trimethylbenzyl.

AMIDES

Amides

Amides includes: *N*-formyl, *N*-acetyl, *N*-chloroacetyl, *N*-trichloroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridyl-carboxamide, *N*-benzoylphenylalanyl derivative, *N*-benzoyl, and *N*-*p*-phenylbenzoyl.

Assisted Cleavage

Assisted cleavage groups include: *N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxphenyl) propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine derivative, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

Cyclic imide derivatives include: *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenyl-maleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted

1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

SPECIAL -NH PROTECTIVE GROUPS

Protective groups for – NH include: *N*-alkyl and *N*-aryl amines, imine derivatives, enamine derivatives, and *N*-hetero atom derivatives (such as *N*-metal, N-N, N-P, N-Si, and N-S), *N*-sulfenyl, and *N*-sulfonyl.

N-Alkyl and *N*-Aryl Amines

N-alkyl and *N*-aryl amines include: *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxyl]-methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolylamine *N* '-oxide.

Imine Derivatives

Imine derivatives include: *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N* ',*N* '-dimethylaminomethylene), *N*,*N* '-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenyl-methylene, and *N*-cyclohexylidene.

Enamine Derivative

An example of an enamine derivative is *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl).

N-Hetero Atom Derivatives

N-metal derivatives include: *N*-borane derivatives, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, and *N*-copper or *N*-zinc chelate. Examples of *N*-*N* derivatives include: *N*-nitro, *N*-nitroso, and *N*-oxide. Examples of *N*-P derivatives include: *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl. Examples of *N*-sulfenyl derivatives include: *N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl,

N-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxy-benzenesulfenyl, *N*-triphenylmethylsulfenyl, and *N*-3-nitropyridinesulfenyl. *N*-sulfonyl derivatives include: *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxy-benzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzene- sulfonyl, *N*-4-methoxybenzenesulfonyl. *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy- 4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)-benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl.

Disclosed compounds which are masked or protected may be prodrugs. compounds metabolized or otherwise transformed *in vivo* to yield a disclosed compound, e.g., transiently during metabolism. This transformation may be a hydrolysis or oxidation which results from contact with a bodily fluid such as blood, or the action of acids, or liver, gastrointestinal, or other enzymes.

Features of the invention are further described in the examples below.

E. EXAMPLES

EXAMPLE 1

[4-Chloro-2-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine (18). (Scheme 2, R_1=Cl, R_2=R_3=H, R_4=CH_3)

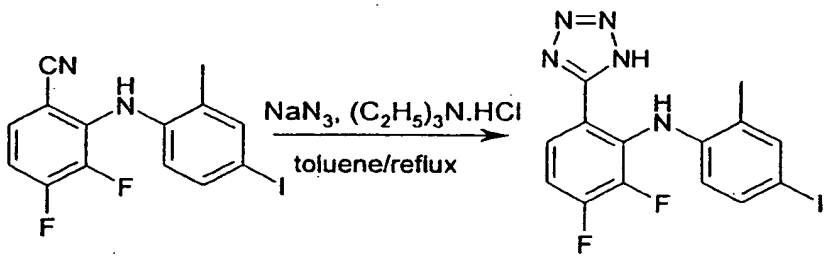
a). A mixture of 5-chloro-2-methoxybenzoic acid 16 (14.8 g, 0.0793 mole) and $SOCl_2$ (28.31 g, 14.97 ml, 0.1584 mole) was refluxed for 2 hours and excess $SOCl_2$ removed leaving a white residue. The solid was dissolved in CH_2Cl_2 and added to a solution of 2-amino-2-methyl-1-propanol (13.98 g, 14.97 ml, 0.1584 mole) in CH_2Cl_2 cooled with ice-bath. The ice-bath was removed, and after stirring at room temperature for 3 hours a white solid precipitated. The precipitate

was separated by filtration and discarded. The filtrate was concentrated leaving a thick colorless oil. $SOCl_2$ (17.4 ml) was added to the oil dropwise. An exothermic reaction took place resulting in to a freely flowing solution. After stirring for 30 minutes, the reaction mixture was poured in to Et_2O (200 ml). An oil separated out. The Et_2O layer was removed by decanting and discarded. The oily residue was dissolved in a minimum amount of water, basified with aqueous 20% NaOH, and extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and concentrated to give **17** as tan oil. Yield 14.63 g (77%).

b). LDA (5 ml of 2.0 M solution in THF) was added to a solution of 4-iodo-2-methylaniline (2.33 g, 0.010 mole) in THF (15 ml) at –78 °C. The mixture was stirred at –78 °C for 30 minutes. To this, a solution of **17** (1.199 g, 0.005 mole) in THF (15 ml) was added. The mixture stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The Et_2O layer was dried ($MgSO_4$) and concentrated to give crude **18** as brown oil. The oil was purified on silica column chromatography. Eluting with CH_2Cl_2 gave pure 1.7 g (77%) of **18** as brown oil. Four hundred and nine milligrams of the oil were dissolved in Et_2O and treated with Et_2O-HCl giving the HCl salt as a light yellow solid precipitate. Yield 356.4 mg (81%); mp 324-330 °C; Anal. Calcd/found for $C_{18}H_{18}N_2OClI \cdot HCl.0.5H_2O$: C, 44.47/44.32; H, 4.15/3.94; N, 5.76/5.66.

EXAMPLE 2

[2,3-Difluoro-6-(1*H*-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine



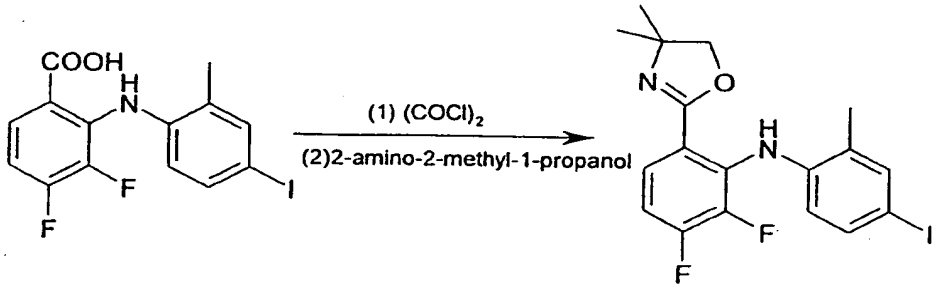
[2,3-Difluoro-6-cyano-phenyl]-(4-iodo-2-methyl-phenyl)-amine (1.11g, 3mmol) and Sodium azide(0.255g, 3.9mmol) and triethylamine hydrochloride (0.537g, 3.9mmol) were all suspended in 10ml toluene and stirred at 100°C for 12 hours. The mixture was concentrated and the residue purified by column chromatography with ethyl acetate/methanol (10/1) to give the product as a foam-like solid. The yield: ~50%

m.p: 83.4-88.7°C

^{1}H NMR($CDCl_3$, 400Hz): δ/ppm 7.69(1H, m, Phenyl-H); 7.42(1H, s, Phenyl-H); 7.27(1H, m, Phenyl-H); 6.91(1H, dd, J=16.2Hz, 8.3Hz, Phenyl-H); 6.40(1H, dd, Phenyl-H); 2.28(3H, s, CH_3)

EXAMPLE 3

[6-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine



A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (1.17g, 3mmol), oxalyl chloride (0.457g, 3.6mmol) in 30ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours then concentrated. The residue was dissolved in 25 ml dichloromethane then the solution was added dropwise to a solution of 2 amino-2-methyl-1-propanol (0.623g, 7mmol) in 25 ml dichloromethane at 0°C, then stirred at room temperature for 12 hours, filtered off the precipitate, the filtration was washed with water, 5% aqueous sodium bicarbonate, 1 N HCl., brine, dried with sodium sulfate. Concentration gave the crude product, then resuspended in 25 ml chloroform, then thionyl chloride was added at 0°C and stirred at room

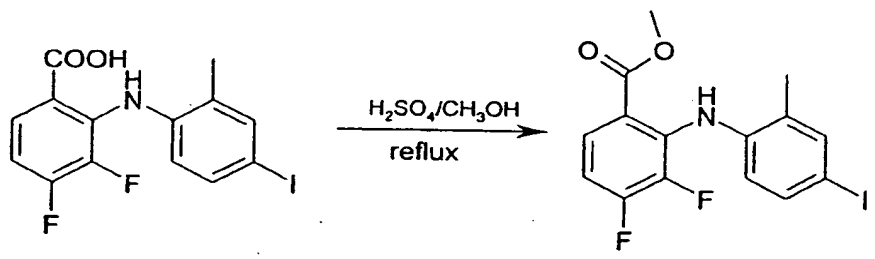
temperature for 15 hours, then concentrated and the residue was dissolved in 30 ml dichloromethane , 1 N HCl was added to adjusted the pH value to 11, the separated and extracted with chloroform, dried with sodium sulfate. Concentrated and then run column with hexanes/dichloromethane (20/1) to give the compound as a white crystal. The yield: 65%

m.p.: 103.7-104.4°C

^{1}H NMR($CDCl_3$, 400Hz): /ppm 10.2(1H, s, NH), 7.48-7.58(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.38(1H, d, J=8.5Hz, Phenyl-H), 6.66-6.72(1H, m, Phenyl-H); 6.58(1H, t, J=8.0Hz, Phenyl-H); 4.01(2H, s, -CH_2-); 2.31(3H, s, Phenyl-CH_3); 1.32(6H, s, -$C(CH_3)_2$-)

EXAMPLE 4

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (5g) was dissolved in 100ml methanol and 5 drops of concentrated sulfuric acid was added, reflux for 4 days. Run column with hexanes/dichloromethane to give the product as a white solid, yield: 50%.

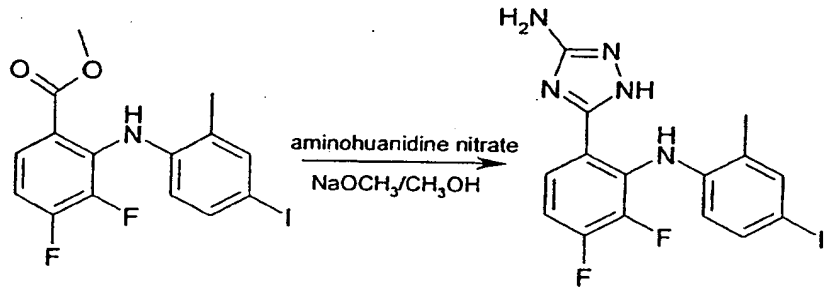
m.p.:90.1-90.4°C

^{1}H NMR($CDCl_3$, 400Hz): /ppm 8.92(1H, s, NH), 7.75-7.78(1H, m, Phenyl-H); 7.49(1H, s, Phenyl-H); 7.38(1H, dd, J=8.5Hz, 2.0Hz, Phenyl-H), 6.66-6.73(1H, m,

Phenyl-H); 6.56-6.60(1H, m, Phenyl-H); 3.88(3H, s, -OC<u>H</u>$_3$); 2.30(3H, s, Phenyl-C<u>H</u>$_3$)

EXAMPLE 5

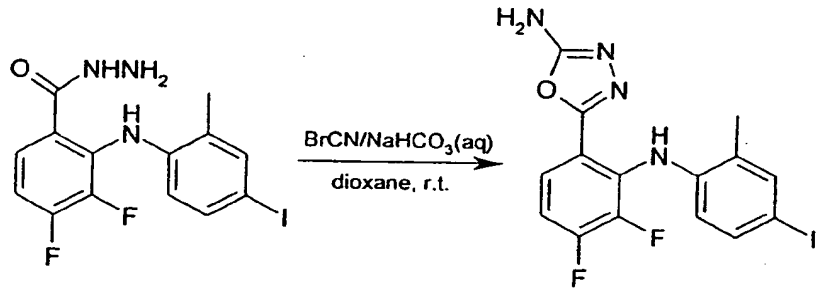
5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazol-3-ylamine



Aminoguanidine nitrate (1.65g, 12mmol) was added to a solution of sodium methoxide (0.648g, 12mmol) in methanol (12ml) at 0°C, then 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid methyl ester was added as a solution of methanol and refulx for 20 hours, concentration and run column with hexanes/ethyl acetate to give the product as a white crystal. The yield: 60%
m.p.: 191.7-192.0°C
^{1}H NMR(DMSO, 400Hz): /ppm 9.45(1H, s, -NH-); 7.79(1H, t, J=7.3Hz, Phenyl-H); 7.51(1H, s, Phenyl-H); 7.35(1H, d, J=10.1Hz, Phenyl-H); 7.05-7.11(1H, m, Phenyl-H); 6.44-6.48(1H, m, Phenyl-H); 6.32(2H, s, -NH$_2$), 2.32(3H, s, CH$_3$)

EXAMPLE 6

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine



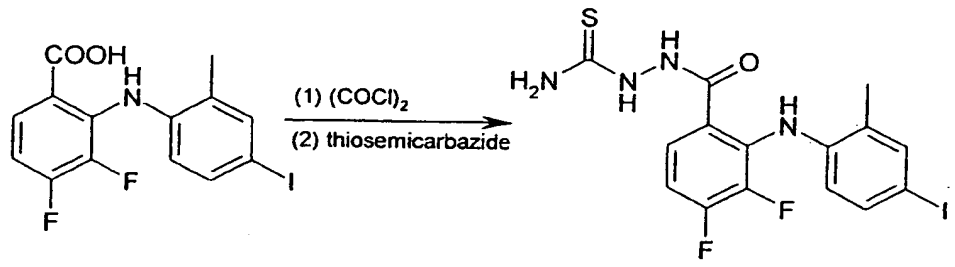
To a solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (0.806g, 2mmol) in 5ml of dioxane was added cyanogen bromide (0.212g, 2mmol) followed by a solution of sodium bicarbonate (0.17g, 2mmol) in 5ml of water. The resulting mixture was stirred 18 ours at room temperature . the solution was concentrated and the residure was run column with hexanes/ethyl acetate (3/1) to give the product which was recrystallized from ethyl acetate / hexanes to provide a pale-yellow crystal. The yield: 58%

m.p.: 183.7-184.0°C

^{1}H NMR($CDCl_3$, 400Hz): / ppm 8.87(1H, s, -NH-); 7.52(1H, s, Phenyl-H); 7.45-7.49(1H, m, Phenyl-H); 7.40(1H, d, J=8.3Hz, Phenyl-H); 6.77-6.83(1H, m, Phenyl-H); 6.60-6.63(1H, m, Phenyl-H); 5.02(2H, s, -NH_2), 2.36(3H, s, CH_3)

EXAMPLE 7

2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]hydrazinecarbothioamide



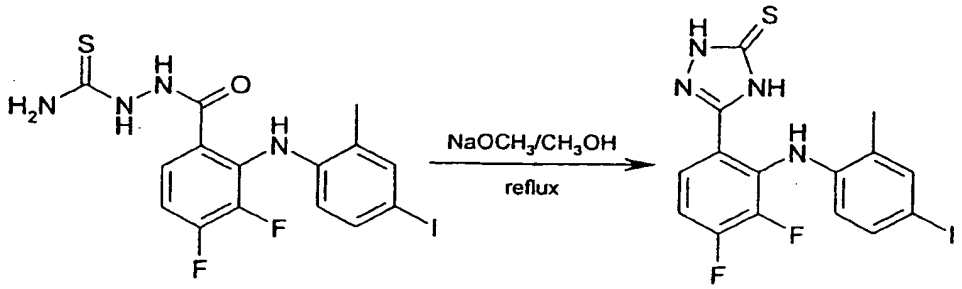
A solution of 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (3.9g, 0.01mol), oxalyl chloride (1.90g, 0.015mol) in 40ml dichloromethane was treated with 2 drops of dimethylformamide, stirred at room temperature for 3 hours before concentration. The residue was dissolved in 10 ml tetrahydrofuran and added to a solution of thiosemicarbazide (2.0g, 0.022mol) in 50ml tetrahydrofuran at 0°C, stirred at room temperature for 14 hours. Concentrated and run column chromatography with hexanes/ethyl acetate (1/1) to give the product as a yellow solid. 2.91g. The yield: 63%

m.p.: 159.5-160.0°C

^{1}H NMR(DMSO, 400Hz): /ppm 10.58(1H, s, -NH-); 9.28(1H, s, -NH-); 8.83(1H, s, -NH-); 7.95(1H, s, Phenyl-H); 7.12-7.75(2H, m, NH_2); 7.51(1H, s, Phenyl-H); 7.37(1H, dd, J=8.6Hz, 1.7Hz, Phenyl-H); 7.16(1H,dd, J=17Hz, 9.0Hz, Phenyl-H); 6.40-6.50(1H, m, Phenyl-H); 5.02(2H, s, -NH_2), 2.00(3H, s, CH_3)

EXAMPLE 8

5-[3,4-Difuoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4*H*-[1,2,4]triazole-3-thiol



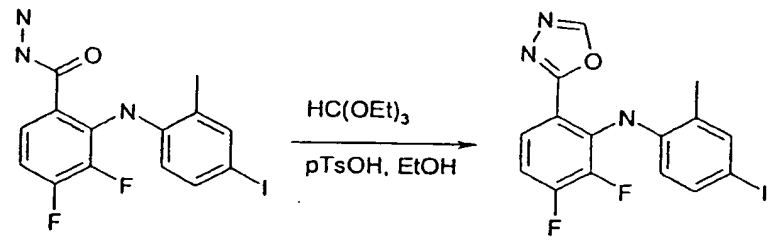
2-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoyl]hydrazinecarbothioamide (1.386g, 3mmol) was dissolved in 15 ml anhydrous methanol, sodium methoxide (25% wt% in methanol) 2.5ml was added at 0°C in one portion. The resulting mixture was heated at reflux for 17 hours before concentration. Run column with hexanes/ethyl acetate to give the product as a needle white crystal. The yield: 40%

m.p.: 196.5(dec.)

^{1}H NMR(DMSO, 400Hz): / ppm 13.87(1H, s, -NH-); 13.80(1H, s, -NH-); 8.16(1H, s, -NH-); 7.61-7.65(1H, m, Phenyl-H); 7.48(1H, s, Phenyl-H); 7.32(1H, dd, J=8.6Hz, 2.2Hz, Phenyl-H); 7.24(1H,dd, J=16.4Hz, 9.5Hz, Phenyl-H); 6.42-6.46(1H, m, Phenyl-H); 5.02(2H, s, -NH_2), 2.20(3H, s, CH_3).

EXAMPLE 9

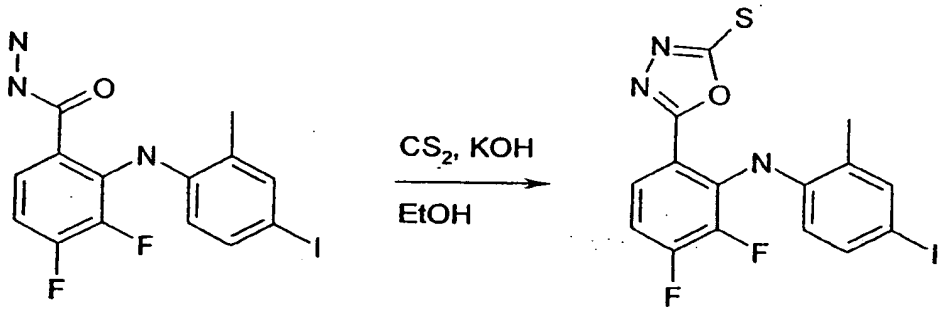
(2,3-Difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (146 mg, 0.36 mmol) was suspended in 7 mL of absolute EtOH and 2 mL of $HC(OEt)_3$ was added along with approximately 3 mg of pTsOH> The reaction was heated to reflux for 3h, cooled and concentration on a rotary evaporator. The reaction was purified (SiO2, 4:1 Hexane/EtOAc) to afford 117 mg (79%) of (2,3-difluoro-6-[1,3,4]oxadiazol-2-yl-phenyl)-(4-iodo-2-methyl-phenyl)-amine as a yellow powder. M.p. = 144.4 – 145.5 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.44 (s, 1H), 7.66 (m, 1H), 7.52 (d, J = 1.7 Hz, 1 H), 7.38 (dd, J = 8.5, 1.9 Hz, 1 H), 6.83 (m, 1H), 6.14 (dd, J = 8.5, 5.9 Hz, 1 H), 2.37 (s, 3 H).

EXAMPLE 10

5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol



3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide (170 mg, 0.42 mmol) was suspended in 7 mL of absolute EtOH and cooled to 0 °C. Carbon disulfide (74 mg, 0.97 mmol) was added followed by 24 mg (0.42 mmol) of powdered KOH. The reaction was stirred for 1 h at 0 °C, 1h at rt, and refluxed for 3 h to afford a homogeneous reaction. The reaction was cooled to rt, at which

point a ppt formed. Water was added and the reaction diluted with 5 mL of EtOAc. 1N HCl was added to acidify the aqueous layer (pH = 2). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated to obtain 96 mg (51%) of 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol as a yellow powder. M.p. = 231.8 – 232.8 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.47 (s, 1H), 7.30 (complex m, 2H), 6.44 (dd, J = 8.0, 4.5 Hz, 1H), 2.19 (s, 3H).

EXAMPLE 11

Cascade assay for inhibitors of the MAP kinase pathway

Incorporation of ^{32}P into myelin basic protein (MBP) is assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contains 20 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 1 mM EGTA, 50,μM [γ-^{32}P]ATP, 10 μg GST-MEK, 0.5 μg GST-MAPK and 40 μg MBP in a final volume of 100 μL. Reactions are stopped after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C filter mat. ^{32}P retained on the filter mat is determined using a 120S Betaplate. Compounds are assessed at 10 μM for ability to inhibit incorporation of ^{32}P.

To ascertain whether compounds are inhibiting GST-MEK or GST MAPK, two additional protocols are employed. In the first protocol, compounds are added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and [γ-^{32}P]ATP. In the second protocol, compounds are added to tubes containing both GST-MEK and GST-MAPK, followed by MBP and [γ-^{32}P]ATP.

Compounds that show activity in both protocols are scored as MAPK inhibitors, while compounds showing activity in only the first protocol are scored as MEK inhibitors.

EXAMPLE 12

In vitro MAP kinase assay

Inhibitory activity can be confirmed in direct assays. For MAP kinase, 1 μg GST-MAPK is incubated with 40 μg MBP for 15 minutes at 30°C in a final volume of 50 μL containing 50 mM Tris (pH 7.5), 10 μM $MgCl_2$, 2 μM EGTA, and 10 μM [γ-^{32}P]ATP. The reaction is stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into MBP is determined by both autoradiography, and scintillation counting of excised bands.

EXAMPLE 13

In vitro MEK assay

For evaluation of direct MEK activity, 10 μg GST-MEK_1 is incubated with 5 μg of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations are 15 minutes at 30°C in a final volume of 50 μL containing 50 mM Tris (pH 7.5), 10 μM $MgCl_2$, 2 , μM EGTA, and 10 μM [γ-^{32}P]ATP. The reaction is stopped by addition of Laemrnli SDS sample buffer. Phosphorylated GST-MAPK-KA is resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA is determined by autoradiography, and subsequent scintillation counting of excised bands. Additionally, an artificially activated MEK containing serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E) is used. When these two sites are phosphorylated, MEK activity is increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this assay, 5 μg GST-MEK-2E is incubated with 5 μg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions are terminated and analyzed as above.

EXAMPLE 14

Whole cell MAP kinase assay

To determine if compounds block activation of MAP kinase in whole cells, the following protocol is used. Cells are plated in multi-well plates and grown to confluence. Cells are serum-deprived overnight. Cells are exposed to the desired concentrations of compound or vehicle (DMSO) for 30 minutes, followed by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells are washed with PBS, and lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates are clarified by centrifugation at 13,000 x g for 10 minutes. Five micrograms of the resulting supernatants are incubated with 10 μg microtubule associated protein-2 (Map2) for 15 minutes at 30°C in a final volume of 25 μL containing 50 mM Tris (pH 7.4), 10 mM $MgCl_2$, 2 mM EGTA and 30 μM [γ-^{32}P]ATP. Reactions are terminated by addition of Laemmli sample buffer. Phosphorylated Map2 is resolved on 7.5% acrylamide gels and incorporated radioactivity is determined by scintillation counting of excised bands.

EXAMPLE 15

Monolayer growth

Cells are plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight hours after seeding, test compounds are added to the cell growth medium and incubation is continued for 2 additional days. Cells are then removed from the wells by incubation with trypsin and enumerated with a Coulter counter.

EXAMPLE 16

Growth in soft-agar

Cells are seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth medium containing 0.3% agar. After chilling to solidify the agar, cells are

transferred to a 37°C incubator. After 7 to 10 days' growth. visible colonies are manually enumerated with the aid of a dissecting microscope.

EXAMPLE 17

Collagen-Induced Arthritis in Mice

Type II collagen-induced arthritis (CIA) in mice is an experimental model of arthritis that has a number of pathologic, immunologic, and genetic features in common with rheumatoid arthritis. The disease is induced by immunization of DBA/1 mice with 100 μg type II collagen, which is a major component of joint cartilage, delivered intradermally in Freund's complete adjuvant. The disease susceptibility is regulated by the class II MHC gene locus, which is analogous to the association of rheumatoid arthritis with HLA-DR4.

A progressive and inflammatory arthritis develops in the majority of mice immunized, characterized by paw width increases of up to 100%. A test compound is administered to mice in a range of amounts, such as 20, 60, 100, and 200 mg/kg body weight/day. The duration of the test can be several weeks to a few months, such as 40, 60, or 80 days. A clinical scoring index is used to assess disease progression from erythema and edema (stage 1), joint distortion (stage 2), to joint ankylosis (stage 3). The disease is variable in that it can affect one or all paws in an animal, resulting in a total possible score of 12 for each mouse. Histopathology of an arthritic joint reveals synovitis, pannus formation, and cartilage and bone erosions. All mouse strains that are susceptible to CIA are high antibody responders to type II collagen, and there is a marked cellular response to CII.

EXAMPLE 18

SCW-induced monoarticular arthritis

Arthritis is induced as described by Schwab, *et al.*, *Infection and Immunity*, 59:4436-4442 (1991) with minor modifications. Rats receive 6 μg sonicated SCW [in 10 μl Dulbecco's PBS (DPBS)] by an intraarticular injection into the right

tibiotalar joint on day 0. On day 21, the DTH is initiated with 100 μg of SCW (250 μl) administered i.v. For oral compound studies, compounds are suspended in vehicle (0.5% hydroxypropyl-methylcellulose/0.2% Tween 80), sonicated, and administered twice daily (10 ml/kg volume) beginning 1 hr prior to reactivation with SCW. Compounds are administered in amounts between 10 and 500 mg/kg body weight/day, such as 20, 30, 60, 100, 200, and 300 mg/kg/day. Edema measurements are obtained by determining the baseline volumes of the sensitized hindpaw before reactivation on day 21, and comparing them with volumes at subsequent time points such as day 22, 23, 24, and 25. Paw volume is determined by mercury plethysmography.

EXAMPLE 19

Mouse ear-heart transplant model

Fey, T.A. *et al.* describe methods for transplanting split-heart neonatal cardiac grafts into the ear pinna of mice and rats (*J. Pharm. and Toxic. Meth.* 39:9-17 (1998)). Compounds are dissolved in solutions containing combinations of absolute ethanol, 0.2% hydroxypropyl methylcellulose in water, propylene glycol, cremophor, and dextrose, or other solvent or suspending vehicle. Mice are dosed orally or intraperitoneally once, twice or three times daily from the day of transplant (day 0) through day 13 or until grafts have been rejected. Rats are dosed once, twice, or three times daily from day 0 through day 13. Each animal is anesthetized and an incision is made at the base of the recipient ear, cutting only the dorsal epidermis and dermis. The incision is spread open and down to the cartilage parallel to the head, and sufficiently wide to accommodate the appropriate tunneling for a rat or insertion tool for a mouse. A neonatal mouse or rat pup less than 60 hours old is anesthetized and cervically dislocated. The heart is removed from the chest, rinsed with saline, bisected longitudinally with a scalpel, and rinsed with sterile saline. The donor heart fragment is placed into the preformed tunnel with the insertion tool and air or residual fluid is gently

expressed from the tunnel with light pressure. No suturing, adhesive bonding, bandaging, or treatment with antibiotics is required.

Implants are examined at 10-20-fold magnification with a stereoscopic dissecting microscope without anesthesia. Recipients whose grafts are not visibly beating may be anesthetized and evaluated for the presence of electrical activity using Grass E-2 platinum subdermal pin microelectodes placed either in the pinna or directly into the graft and a tachograph. Implants can be examined 1-4 times a day for 10, 20, 30 or more days. The ability of a test compound to ameliorate symptoms of transplant rejection can be compared with a control compound such as cyclosporine, tacrolimus, or orally-administered lefluonomide.

EXAMPLE 20

Murine ovalbumin-induced eosinophilia

Female C57BL/6 mice are obtained from the Jackson Laboratory (Bar Harbor, ME). All animals are given food and water ad libitum. Mice are sensitized with a single i.p. injection of OVA (grade V, Sigma Chemical Company, St. Louis, MO) adsorbed to alum, (10 μg OVA + 9 mg alum in 200 μl saline) or vehicle control, (9 mg alum in 200 μl saline) on day 0. On day 14, the mice are challenged with a 12-minute inhalation of an aerosol consisting of 1.5% OVA (weight/volume) in saline produced by a nebulizer (small particle generator, model SPAG-2; ICN Pharmaceuticals, Costa Mesa, CA). Groups of eight mice are dosed with oral vehicle (0.5% hydroxypropylmethylcellulose / 0.25% TWEEN-80), or a test compound at 10, 30, or 100 mg/kg in oral vehicle, 200 μl per mouse p.o. Dosing is performed once per day starting on day 7 or day 13, and extending through day 16.

For determination of pulmonary eosinophilia, three days after the first OVA aerosol challenge (day 17), the mice are anesthetized with an i.p. injection of anesthetic (Ketamine/Acepromazine/Xylazine), and the tracheae is exposed and cannulated. The lungs and upper airways are lavaged twice with 0.5 ml of cold PBS. A portion (200 μl) of the bronchoalveolar lavage (BAL) fluid is enumerated using a Coulter counter Model ZB1 (Coulter Electronics, Hialeah, FL). The remaining BAL fluid is then centrifuged at 300 x g for five minutes, and the cells are resuspended in 1 ml of HBSS (Gibco BRL) containing 0.5% fetal calf serum (HyClone) and 10 mM HEPES (Gibco BRL). The cell suspension is centrifuged in a cytospin (Shandon Southern Instruments, Sewickley, PA) and stained by Diff Quick (American Scientific Products, McGraw Park, IL) to differentiate BAL leukocytes into neutrophil, eosinophil, monocyte or lymphocyte subsets. The number of eosinophils in the BAL fluid is determined by multiplying the percentage of eosinophils by the total cell count.

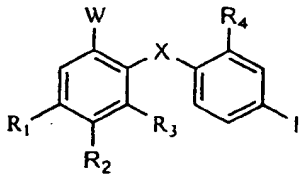
F. OTHER EMBODIMENTS

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

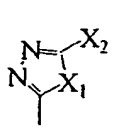
CLAIMS

1. A compound of formula (I):



(I)

W is one of the following formulae (i) – (xiii):



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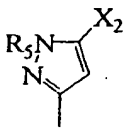

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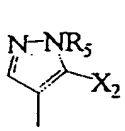
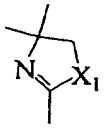
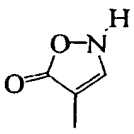


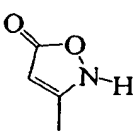
(iii)



(iV)



(v)



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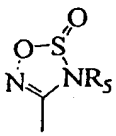

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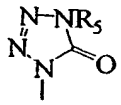

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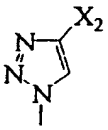

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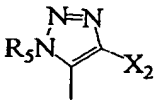

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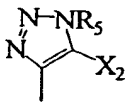

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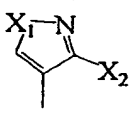

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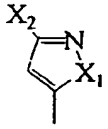

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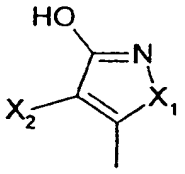

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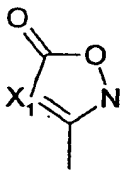

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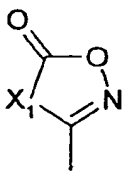

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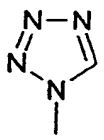

(xvii)

X_1 is O, S, or NR_F;

X_2 is OH, SH, or NHR_E;

each of R_E and R_F is H or C $_{1-4}$ alkyl;

each of R_1 and R_2 is independently selected from H, F, NO_2, Br and Cl; R_1 can also be $SO_2NR_GR_H$, or R_1 and R_2 together with the benzene ring to which they are attached constitute an indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthioazole;

R_3 is H or F;

each of R_G, R_H, and R_4 is independently selected from H, Cl and CH_3;

R_5 is H or C $_{3-4}$ alkyl; and

wherein each hydrocarbon radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, hydroxyl, amino, (amino)sulfonyl, and NO_2; and

wherein each heterocyclic radical above is optionally substituted with between 1 and 3 substituents independently selected from halo, C $_{3-4}$ alkyl, C $_{3-6}$ cycloalkyl, C $_{3-4}$ alkenyl, C $_{3-4}$ alkynyl, phenyl, hydroxyl, amino, (amino)sulfonyl, and NO_2, wherein each substituent alkyl, cycloalkyl, alkenyl, alkynyl or phenyl is in turn optionally substituted with between 1 and 2 substituents independently selected from halo, C $_{1-2}$ alkyl, hydroxyl, amino, and NO_2;

or a pharmaceutically acceptable salt or C $_{1-8}$ ester thereof.

2. A compound of claim 1, wherein R_1 is bromo or chloro.

3. A compound of claim 1, wherein R_2 is fluoro.

4. A compound of claim 1, wherein R_3 is H.

5. A compound of claim 4, wherein each of R_2 and R_3 is H.

6. A compound of claim 1, wherein each of R_2 and R_3 is fluoro.

7. A compound of claim 6, wherein R_1 is bromo.

8. A compound of claim 6, wherein R_1 is fluoro.

9. A compound of claim 1, wherein R_2 is nitro.

10. A compound of claim 8, wherein R_3 is H.

11. A compound of claim 1, wherein R_4 is chloro.

12. A compound of claim 1, wherein R_4 is methyl.

13. A compound of claim 1, wherein R_5 is H.

14. A compound of claim 1, wherein R_5 is CH_3.

15. A compound of claim 1, wherein X_1 is O or S.

16. A compound of claim 1, wherein X_1 is NH or NCH_3.

17. A compound of claim 1, wherein X_2 is OH, SH, or NH_2.

18. A compound of claim 1, wherein X_2 is $NHCH_3$ or OH.

19. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically-acceptable carrier.

20. A compound of claim 1, having a structure: [5-fluoro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)- amine; (4-iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3,4-trifluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [4-bromo-6-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,3-difluoro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-5-fluoro-4-nitro-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ol; or 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ol.

21. A compound of claim 1, having a structure:
5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-

[1,3,4]thiadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazol-2-ylamine; 5-[4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazol-2-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazol-3-ylamine; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]thiadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-[1,3,4]oxadiazole-2-thiol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-[1,2,4]triazole-3-thiol; or 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-[1,2,4]triazole-3-thiol.

22. A compound of claim 1, having a structure: 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isothiazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-isoxazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1-methyl-1H-pyrazol-3-ol; or 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1-methyl-1H-pyrazol-3-ol.

23. A compound of claim 1, having a structure: 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-3,4,5-trifluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-5-bromo-3,4-difluoro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[2-(2-amino-4-iodo-phenylamino)-4-fluoro-5-nitro-phenyl]-1-methyl-1H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 3-methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3H-[1,2,3]triazol-4-ol; 5-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 5-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 2-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-pyrazol-3-ol; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2-methyl-2H-pyrazol-3-ol; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2-methyl-2H-pyrazol-3-ol; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1,4-dihydro-tetrazol-5-one; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4-methyl-1,4-dihydro-tetrazol-5-one; 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; 1-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-1H-[1,2,3]triazol-4-ol; or 1-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-1H-[1,2,3]triazol-4-ol.

24. A compound of claim 1, having a structure: 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3[3,4-difluoro-2-(4-iodo-2-

methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-2H-isoxazol-5-one; 3-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-2H-isoxazol-5-one; [5-fluoro-2-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-amine; [4-bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; [5-fluoro-4-nitro-2-(2-oxo-2,3-dihydro-2I>4_-[1,2,3,5]oxathiadiazol-4-yl)-phenyl]-(4-iodo-2-methyl-phenyl)-amine; 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; 4-[5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-4H-isoxazol-5-one; or 4-[4-fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-4H-isoxazol-5-one.

25. A method for treating a proliferative disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

26. A method of claim 25, wherein said proliferative disease is selected from psoriasis, restenosis, autoimmune disease, and atherosclerosis.

27. A method for treating cancer, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

28. A method of claim 27, wherein said cancer is MEK-related.

29. A method of claim 27, wherein said cancer is brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer.

30. A method for treating, or ameliorating the sequelae of, a stroke, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

31. A method for treating, or ameliorating the sequelae of, heart failure, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

32. A method for treating or reducing the symptoms of xenograft rejection, said method comprising administering to an organ transplant, limb transplant, skin transplant, cell(s) transplant, or bone marrow transplant patient a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

33. A method for treating osteoarthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

34. A method for treating rheumatoid arthritis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

35. A method for treating cystic fibrosis, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

36. A method for treating hepatomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

37. A method for treating cardiomegaly, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

38. A method for treating Alzheimer's disease, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

39. A method for treating a complication of diabetes, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

40. A method for treating septic shock, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

41. A method for treating a viral infection, said method comprising administering to a patient in need of such treatment a pharmaceutically-effective amount of a composition comprising a compound of claim 1.

42. A method of claim 41, wherein said infection is an infection of HIV.

43. A method for treating cancer, said method comprising (a) administering to a patient in need of such treatment, a pharmaceutically-effective amount of a composition comprising a compound of claim 1; and (b) administering a therapy selected from radiation therapy and chemotherapy.

44. A method of claim 43, wherein said chemotherapy comprises a mitotic inhibitor.

45. A method of claim 44, wherein said mitotic inhibitor is selected from paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, and vinflunine.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 99/30416

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/10 C07D257/04 A61K31/41 C07D249/14 A61K31/4196
C07D271/113 A61K31/4245 C07D249/12 A61P37/02 A61P31/18
A61K31/421

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 01421 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) see especially compound examples 207,208,209 the whole document	1-45
A	WO 96 22985 A (WARNER LAMBERT CO) 1 August 1996 (1996-08-01) the whole document	1-45
P,Y	WO 99 01426 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) the whole document	1-45

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2000	07 April 2000 (07.04.00)

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Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 99/30416

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) see examples 207,208 and 209 and whole document	1-45

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/US 99/30416

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

As there is no definition for X in either the claims or the description, it has been searched as if it were NH, as all examples have NH linking the two phenyl rings.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1(part)

As there is no definition for X in either the claims or the description, it has been searched as if it were NH, as all examples have NH linking the two phenyl rings.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 99/30416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9901421 A	14-01-1999	AU 8262698 A	25-01-1999
		HR 980369 A	30-04-1999
WO 9622985 A	01-08-1996	US 5525625 A	11-06-1996
		AT 181913 T	15-07-1999
		AU 690400 B	23-04-1998
		AU 4245696 A	14-08-1996
		CA 2208075 A	01-08-1996
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		DE 69510696 T	23-12-1999
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		JP 10512878 T	08-12-1998
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		ZA 9600528 A	15-08-1996
WO 9901426 A	14-01-1999	AU 8262798 A	25-01-1999
		HR 980368 A	30-04-1999
		NO 996491 A	29-12-1999
WO 9837881 A	03-09-1998	AU 5610398 A	18-09-1998
		ZA 9801578 A	02-09-1998

Form PCT/ISA/210 (patent family annex) (July 1992)

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